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Assessment of Breast Cancer Prevention Practices among Women Attending Primary Health Care in Abha City, Aseer Region, Saudi Arabia

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Abstract

Cancer is a leading cause of death worldwide, with breast cancer being the most common (2.26 million new cases and 685,000 deaths). In Saudi Arabia, breast cancer ranked the first among females in 2014, accounting for 15.9% of all cancers reported among Saudi nationals and 28.7% of all cancers reported among females of all ages. Early detection of breast cancer could decrease the risks, have a better prognosis, and have better outcomes/more successful treatments. Prevalence of breast cancer reached more than 25% of all diagnosed cancer in the kingdom among women. **Aim:** This study aims to assess the knowledge and performance of women attending primary care centers about breast self-examination and mammogram screening for prevention and early detection of breast cancer in Abha city primary healthcare centers, Kingdom of Saudi Arabia. **Research Method:** cross sectional design was conducted by using questionnaire, which was distributed to primary care center nurses. The collected data was statistically analyzed using the Statistical Package for Social Sciences, version 25. **Results:** The study found that partic-

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ipants had poor awareness and knowledge about breast self-examination, risk factors for breast cancer, and trends and practices in early diagnosis of breast cancer. **Conclusion and Recommendations:** It recommends increasing awareness campaigns and providing educational programs to improve knowledge and practices.

Keywords

Assessment, Breast Cancer, Prevention Practices, Women Attending, Health Care Centers, Abha City

1. Introduction

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, with breast cancer being the most common (2.26 million new cases and 685,000 deaths) [1]. Generally, the breast cancer rate is higher in developed than developing countries. This difference may be due to relatively low awareness, screening practices, and diagnoses in developing countries. Nevertheless, the rates are increasing rapidly in many developing countries [2]. Breast cancer remains the leading cause of death among Saudi women. It has a significant impact on the health of women worldwide, and the Saudi Arabia is no exception [3].

In Saudi Arabia breast cancer ranked first among females in 2014. It accounted for 15.9% of all cancers reported among Saudi nationals and for 28.7% of all cancers reported among females of all.

Early detection of breast cancer could decrease the risks, is more likely to have a better prognosis, and a better outcomes/more successful treatments. On the other hand, a delayed diagnosis of breast cancer, and consequently worse prognosis, have been attributed to lack of awareness toward breast cancer risks or presence of barriers limiting women to utilize healthcare services. The prevalence of breast cancer reached more than 25% of all diagnosed cancer in the kingdom among women [4].

Lack of knowledge toward breast cancer risks and low utilization of mammogram are reported among women in Saudi Arabia. Therefore, the role of primary healthcare centers regarding practices to prevent breast cancer is crucial. Health education about breast cancer prevention could decrease the burden of breast cancer risks [5]. What might be achieved through implementation of strategies for primary prevention? These strategies include increasing the awareness of women about breast cancer major risk factors, such as, adherence of healthy lifestyle habits, lower their weight, breastfeeding, to be physically active, and preventing alcohol consumption [6].

Moreover, women aged 50 years should start biennial mammograms and to continue till the age of 74 years. Selective screening is to be applied for younger women aged 40 - 49 years based on individual factors. There is need of protec-

tion motivational theory among the female to diagnose the breast cancer at early stage. As there is lack of knowledge about the BSE among the primary healthcare therefore it is needed to educate and train them that they motivate the female to assess themselves which help in the cancer prevention [7].

Breast cancer self-examination is commonly done among the patients who have the history of breast cancer in the family. Primary healthcare that has good knowledge about the breast cancer and it prevalent, practice the self-examination more frequently than the nurses who do not have knowledge about the breast cancer [8]. The self-examination regarding the breast cancer is one of the costs friendly as there is no need of equipment or tools to assess the breast cancer. Breast cancer self-assessment is painless, safe, and easy to assess regularly to identify any lymph in the breast at the early stage of diseases [9]. Moreover, the education is also the factor associated with the breast cancer self-examination among the females. As nursing staff reported that female with the enough educational background easily learn the self-examination as compare to the female with the no education [10].

Up to our knowledge no study was conducted regarding knowledge and performance of women attending primary care centers about breast self-examination and mammogram screening for prevention and early detection of breast cancer in Abha city primary healthcare centers. So, this study purpose is to assess knowledge and performance of women attending primary care centers about breast self-examination and mammogram screening for prevention and early detection of breast cancer in Abha city primary healthcare centers, Kingdom of Saudi Arabia.

1.1. Problem Statement

In Saudi Arabia, breast cancer is the leading cause of death among women [11]. Its incidence is increasing rapidly in many developing countries [12]. Therefore, its prevention and early detection are associated with decreased risks, better prognosis, and more successful treatments [13].

Moreover, female who are homemakers do not have enough information and knowledge about the breast cancer self-examination that's why cancer is common among the female in the world. Mortality rate is also high among the female with the breast cancer as late diagnosed of the cancer lead toward the death. Therefore, it is needed to develop the awareness as well as training program for the female who are homemakers as well as those who doesn't have enough education or knowledge about the BSE.

We are unaware of any studies on the trends and practices of women visiting primary care institutions about mammogram screening and breast self-examination for prevention and early detection of breast cancer. Therefore, the objective of this study is to assess the knowledge and behavior of female primary care center patients in Abha City, Kingdom of Saudi Arabia, regarding breast self-examination and mammography screening for breast cancer prevention and early detection.

1.2. Background of Study

Breast cancer is the most prevalent type, accounting for 2.26 million new cases and 685,000 fatalities globally from cancer, breast cancer was the most common type of cancer among women in Saudi Arabia in 2014, making up 15.9% of all cancer cases reported [14]. Early identification of breast cancer may result in lower risks, a better prognosis, and more effective results and therapies.

Primary healthcare facilities are vital for preventing breast cancer because women in Saudi Arabia are reported to lack awareness and use mammograms seldom [15]. By raising women's understanding of the primary risk factors for breast cancer, for example, health education about breast cancer prevention might reduce the burden of breast cancer risks [16]. Mammograms for women should begin at age 50 and continue every two years until they are 74. For younger women between the ages of 40 and 49, selective screening will be used depending on individual criteria. Patients with a family history of breast cancer frequently perform breast cancer self-examinations, and primary care providers who are knowledgeable about breast cancer and its prevalence perform breast cancer self-examinations more frequently than nurses who lack this information. To detect any breast lymph at the early stages of diseases, routine assessment is painless, safe, and simple [17].

As far as we are aware, no research has been done on the trends and practices of women visiting primary care facilities about breast self-examination and mammography screening for prevention and early detection of breast cancer. Therefore, the goal of this study is to evaluate the knowledge and performance of female primary health care patients regarding breast self-examination and mammography screening for breast cancer prevention and early detection in Abha City, Kingdom of Saudi Arabia.

1.3. Purpose of Study

General Objective: This study aims to assess knowledge and performance of women attending primary care centers about breast self-examination and mammogram screening for prevention and early detection of breast cancer.

Specific Objectives:

- To assess awareness of women attending primary care centers in Abha City, Aseer Region, KSA about breast self-examination.
- To explore trends and practices of women attending primary care centers in Abha City, Aseer Region, KSA about mammogram screening.
- To explore the correlation between knowledge, trends and practices of women attending primary care centers in Abha City, Aseer Region, KSA about mammogram screening.

1.4. Research Questions

- What is the awareness prevalence of women attending primary care centers in Abha City, Aseer Region, KSA about breast self-examination?

- What are the trends and practices of women attending primary care centers in Abha City, Aseer Region, KSA about mammogram screening?
- What is the correlation between knowledge, trends and practices of women attending primary care centers in Abha City, Aseer Region, KSA about mammogram screening?

1.5. Definition or Concepts of Terms

- **Mammogram screening:** Breast X-rays are used to look for breast cancer in the absence of symptoms or indicators [18].
- **Breast self-examination:** By feeling for lumps or other changes, a person can examine their own breasts. Self-examinations of the breasts can teach a person how they typically feel and appear and help them recognize when changes take place [19].
- **Primary health care centers**: A community-wide health-care system known as primary healthcare focuses on solving human problems as early as possible along the continuum from health promotion and disease prevention to treatment, rehabilitative services, and pain management, and as practically as is possible from where people live and work. It strives to guarantee their own equitable distribution, as well as the best possible health outcomes [20].
- **Risk factors**: Characteristics or circumstances that increase the likelihood of experiencing a negative event or developing a specific problem or illness. In diverse contexts, such as health, finances, and safety [21].
- **Level of awareness:** Refers to the extent to which individuals or a group is aware, informed, or knowledgeable about a specific topic, issue, or situation [22].
- **Prevention practices:**

Prevention practices are measures, actions, or strategies taken to prevent or mitigate the occurrence, impact, or spread of problems, hazards, diseases, or other undesirable events.

1.6. Significance to Nursing

It will help healthcare institutions to develop the training programs among the female primary healthcare to spread the knowledge about the self-examination about the breast cancer prevention. While nursing education and training would be improved by using certain steps accordingly.

1.7. Summary

Breast Cancer is leading heath taking disease. As this disease having roots in around the globe. That's why assessment and prevention of breast cancer is most valuable and interesting topic in the literature. This section presented the statement of problem and background about breast cancer self-examination and mammogram screening. The next section will represent the framework of research and previous studies related to breast cancer self-examination and

mammogram screening.

2. Literature Review

In this part, reference will be made to represent previous studies related to breast cancer self-examination and mammogram screening. As from each corner of the world, many of the research literature are available. For this, we focused on general to specific approach, as we focused first on international, local and national studies. To search out, we use Google scholar and Google search engine by using targeted variables.

2.1. Conceptual Model, Theory, or Framework

The "Health Belief" Model will be applied to this study. This model has been identified as one of the approaches used to assess individual's anxieties and fear about their health, their ability to follow healthcare advice and how they relate with health professionals within the healthcare facility. Two important components have been identified to affect persons' choice of a recommended health behavior in the model, *i.e.*, knowledge and belief about susceptibility to breast cancer and its severity. However, availability, affordability, and accessibility to health services as well as clients' attitude can be possible barriers that may impede prevention of breast cancer and early detection services. It is expected that an increased understanding of the benefit of early detection and availability of essential resources, in the context of a favorable environment may increase screening rates, leading to early detection of breast cancer. The study also drew from the diffusion of innovation "behavioral theory", which provides the grounds to adopt methods for the quick dissemination and uptake of new programs in breast cancer prevention and early detection into communities through patients, families, and micro-communities [23] (**Figure 1**).

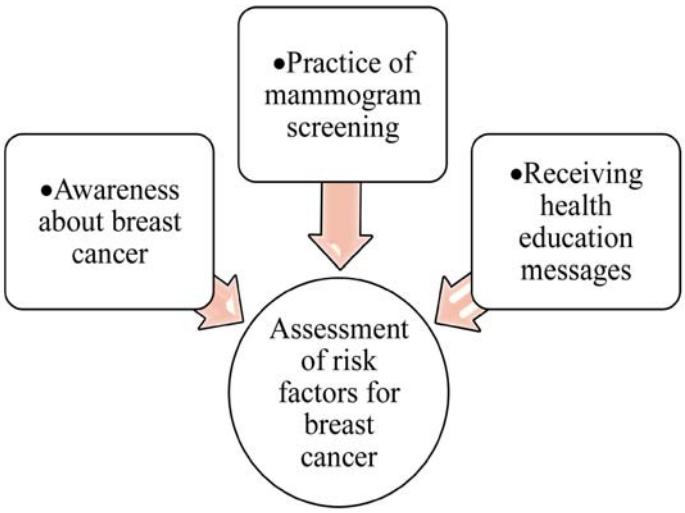

Figure 1. The impact of assessment of risk factors for breast cancer on awareness, practices, and health education programs as outcome variables.

2.2. Evaluation of Evidence

[24] conducted a cross sectional study among women in Riyadh, Saudi Arabia to assess their awareness of breast cancer risks and mammogram screening. It was reported that most of the participants (68%) knew about the warning signs of breast cancer (bleeding or nipple' discharge). Approximately 75.8% had a good knowledge about breast cancer risk factors, but 24.4% had a poor knowledge level. Almost 60.9% knew about BSE and mammography utilization are the methods for early detection of breast cancer.

[25] carried out a cross sectional study among college women to assess their awareness of breast cancer preventive methods and risk reduction. The study results showed that most women knew about the risk factors of breast cancer obesity (72%), menopausal hormone therapy (68%), childbearing after age 35 (63%), and alcohol consumption (52%).

Qualitative research was carried out to examine the breast cancer self-examination among the Ghana female's healthcare. The themes suggested that there is lack of screening tools for BSE, there is lack of training among the female healthcare providers, there is lack of awareness among the population and women negative attitude toward the self-examination. The research suggested that breast cancer is prevalent among the female due to lack of resources by using it to control the cancer among them. It also suggested that training or awareness session given by the nursing staff may increase the BSE and decrease the risk of breast cancer.

Nursing staff approximating less than 10% execute the assessment for breast cancer self-examination among the female patient cause of lack of knowledge as well as training as the research suggested that nurses without the minimum education about the assessing the breast cancer, more likely to increase risk of cancer among the patients [26].

Moreover the breast cancer is not only prevalent in the female but the men as well as the lack of self-awareness and understanding regarding breast cancer and it symptoms. Breast cancer's early detection help in getting it worse among the female. The early stage of breast cancer diagnosed if the patients are habitual of self-assessment regarding it. The self-assessment is commonly practices among the female who have family history of breast cancer or any kind of cancer [27].

The self-examination regarding the breast cancer is one of the costs friendly as there is no need of equipment or tools to assess the breast cancer. Breast cancer self-assessment is painless, safe and easy to assess regularly to identify any lymph in the breast at the early stage of diseases. Breast cancer self-examination minimize the risk of cancer [28].

Furthermore, a cross sectional study was carried out by [29] to examine the female breast cancer cares. The result suggested that female who does not have information and insight about the breast cancer, they find the lymph but wait to increase in its size and when it increases in size they indulge in the denial phase as it is not the cancerous lymph which pushes them toward the cancer.

Also, the breast cancer self-examination among the students is also important factor to prevent it at early stage. Research was conducted to see the students' awareness about the BSE which was quite negative but after the training about the BSE, it was found that they were able to self-evaluate about the breast cancer. The training and awareness about the breast cancer decrease the prevalence chances among the patients as well as increase the knowledge about the BSE [30].

A previous study was conducted in Saudi Arabia among women to assess their awareness of breast cancer, risk factors and its reduction/prevention. In adequate awareness was reported among women concerning breast cancer warning signs, risk factors, and breast self-efficiency to reduce the breast cancer risks which were associated with their marital status, occupational status, and the educational level. Likewise, the younger female is more aware of breast cancer and they frequently assess themselves as there are multiple factors associated with the breast cancer, most important factor is genetic factor associated with the breast cancer. As the research suggested that there is gap of knowledge about the breast cancer self-examination among the older females. As it is observed that breast cancer is prevalent among the older female than the younger one.

In the KSA, female is reluctant to use the tools such as mammography as they consider it painful due to which they avoid the examination of breast cancer therefore there is increase in the cancer. The self-examination is easy for them to evaluate themselves at the early stage of any lymph which prevents the further cancer among them. The mammography is reported as costly to examine daily, weekly or monthly basis. As compared to it self-examination is effective and time consuming.

As a study of [31] showed there is positive attitude toward the breast cancer self-examination among the female in KSA. The study was carried out to see the attitude and awareness of female about the breast cancer. The result suggested that after the awareness program giving by the nursing staff among the female had positive impact on their attitude toward the BSE. Mass media has an important role in spreading the breast cancer self-examination awareness programs and public service messages and also its prevention among the young female.

2.3. Summary

The second section dealt with previous studies and literature related to breast cancer self-examination and mammogram screening. In the third section, the method of conducting the study and the administration used for the study will be discussed in detail.

3. Methodology

Introduction

This section discusses the study design, data gathering procedure, and sample selection including inclusion and exclusion criteria, study instrument and statis-

tical treatment of data.

3.1. Identification of Design

Cross-sectional study design, which serves assessing the prevalence or magnitude of a research point of interest, e.g., disease, knowledge, or practice among participants. A cross-sectional study has the advantage of enabling researchers to compare a wide range of factors.

3.2. Target Group or Aggregate

The target group of this research was the women attending primary care centers at Abha City. The women in the target group were selected using a convenience sampling method. Convenience sampling is a non-probability sampling technique in which participants are selected on the basis of their availability and willingness to participate. In this case, women who were attending primary care centres in Abha city and met the inclusion criteria were selected. The required study sample was determined based on the inclusion and exclusion criteria from a totally 384 women attending primary care centers by using Open-Epi program at a confidence level at 95%, margin of error 5%, response distribution 50%.

3.3. Inclusion Criteria

- Willing to participate in the study.
- Women (aged >17 years), who attend the study settings.
- Those who do not have breast cancer.

3.4. Exclusion Criteria

- Those with confirmed diagnosis of breast cancer.
- Those who are not willing to participate.

4. Methodology

The study was conducted at Primary health care centers, Abha City, Aseer Region, Saudi Arabia.

4.1. Plan and Implementation Process

Data were collected in 3 months. Before starting the study, written permission was obtained from Institution Review Board Standing Committee at Hail University (H-2023-024). Then, with the approval of the Migration and Refugee Board, of the Provincial Directorate of Health in Aseer Province, data collection permission was obtained. While from the participants, written consent was obtained by briefly stating the purpose of the study. By signing an informed consent form, the participant will be able to participate in the study. The questionnaire was distributed through a Google form, where this was done in cooperation with nurses in health centers and in cooperation with managers in health centers to facilitate the task in the presence of the researcher, where the re-

searcher collected data, set coding, and stored all data in the password-protected drive. Further data analysis was carried out according to the research requirements.

4.2. Study Instrument

A study questionnaire was developed in a simple Arabic language. It was adapted from those used by similar studies. The study questionnaire comprises the following parts:

1) Personal characteristics (8 questions): Age, having regular menses, marital status, absolute breastfeeding practices, educational status, employment status, average monthly family income, and residence.

2) Awareness about breast cancer (6 questions): Having heard about breast cancer, sources of information about breast cancer, knowing a woman that has been diagnosed of breast cancer, screening methods, risk factors, and symptoms of breast cancer.

3) Assessment of risk factors for breast cancer (14 questions): Age at menarche, age at marriage, age at first pregnancy, number of pregnancies and abortions, number of children, use of hormonal contraceptives, family history of cancer breast, practice of physical activity, and smoking status.

4) Trends and screening practices for breast cancer (12 questions): Age at start of BSE, being vulnerable to breast cancer, benefits of early diagnosis of breast cancer, advising others to perform BSE, what has been done for early diagnosis of breast cancer, intention to perform BSE in the future, sources of advice to perform BSE, frequency of performing BSE, how to perform BSE, and reasons for not performing BSE.

5) Practice of mammogram screening.

6) Receiving health education messages related to breast cancer prevention during their visits to the primary health care centers.

4.3. Scoring and Grading of Responses

A score was assigned for each positive awareness item, good practice response and a performed screening practice, and a score of (0) was assigned for each negative awareness item. The total scores for awareness, trends , risks and practice will be summed up, then the percent total score of each was calculated by dividing (total score × 100)/(maximum score).

Participants' grades of awareness toward breast cancer were decided as follows: (33).

- Poor awareness: <15%;
- Moderate awareness: 15% - 25%;
- Good awareness: >25%.

Participants' trends and practices regarding early diagnosis of breast cancer was decided as follows:

- Poor: <25%;
- Good: ≥25%;

Risk factors for breast cancer will be decided as follows:

- Less risk factor: <15%;
- Moderate risk factor: 15% - 25%;
- High Risk factor awareness: >25%.

4.4. Validity and Reliability

In order to ensure the validity and reliability of the questionnaire, several steps were taken. First, the questionnaire was modified from questionnaires previously used in similar studies conducted. This adaptation process included reviewing previous questionnaires and modifying and adding questions to align with the objectives of the current study. In addition, the questionnaire was translated into simple Arabic to ensure comprehensibility and suitability for the target population. The translation process included input from bilingual experts to ensure accurate translation and cultural appropriateness.

The validity of the questionnaire was evaluated by conducting a pilot test on a small sample of women attending primary care centers in the city of Abha. This pilot test helped identify any ambiguity or difficulties in understanding the questions and allowed for the necessary modifications to be made.

Regarding content validity, the questionnaire was reviewed by experts in the field of breast cancer prevention. The questionnaire was evaluated to ensure that it adequately covers aspects relevant to breast cancer prevention and that the questions are clear and appropriate for the target population. Internal consistency, which measures the extent to which questions in the questionnaire relate to each other, was assessed through measures such as Cronbach's alpha, where a high Cronbach's alpha indicates that the questions in the questionnaire are measuring the same underlying construct.

4.5. Ethical Consideration

Furthermore, the purpose of the study was explained to the participants, and it was stressed that the information is confidential and that participation in the study is voluntary.

4.6. Summary

In the third section, the method of conducting the study, the tool used in the study, in addition to the study criteria and data extraction, data management, plan and implementation process, and everything related to the method, were discussed, and this was summarized in detail, as this explains everything that has been done.

5. Project Outcomes

The fourth section would include a description of the results of the study and answering the study questions. The results would be presented in tables and comments on the results.

Table 1 shows the Sociodemographic characteristics, there were (384) participants participated in our study, regarding to the Age, most of our participants from the age (28 - 38 years) (34.6%). Moreover, (54.4%) had regular menstrual cycle and (53.1%) were married. Only (25.8%) had Practice exclusive breastfeeding of your children for at least 6 months to all children. (26.8%) from our

Table 1. Frequencies and percentages regarding socio demographic characteristics.

	N	%
Age		
17 - 27	71	18.5
28 - 38	133	34.6
39 - 49	62	16.1
50 - 60	50	13.0
more than 60	68	17.7
Is the menstrual cycle regular?		
Yes	209	54.4
No	175	45.6
Familial status		
Single	156	40.6
Married	204	53.1
Divorced	18	4.7
Widowed	6	1.6
Practice exclusive breastfeeding of your children for at least 6 months		
Yes to all children	99	25.8
No to all children	198	51.6
Yes for some children	87	22.7
Educational level		
Illiteracy	64	16.7
Primary	121	31.5
Middle	51	13.3
Secondary	45	11.7
Collegiate	103	26.8
Job status		
Work	193	50.3
Not Work	191	49.7
Average monthly household income (SR)		
Less than 10,000	111	28.9
10,000 - 20,000	182	47.4
More than 20,000	91	23.7
Living		
City	180	46.9
Village	204	53.1

participants had Collegiate degree. There were (50.3%) were worked and (49.7%) not work. Regarding to the average monthly household income (SR), (47.4%) from our participants (10,000 - 20,000), and most of them lived in the village (53.1%).

Table 2 shows that (88.5%) had poor awareness about breast self-examination, and (11.5%) had moderate awareness about breast self-examination.

Table 3 shows that there were (68.5%) from our participants had less risk factors regarding the breast cancer, (24.5%) and (1.0%) had moderate and high risk factors regarding breast cancer respectively.

Table 4 shows that more than half of the study participants heard about breast cancer. In addition, the main source of knowledge is social media and books. However, the least source of knowledge is health care professionals. Likewise, 48.7% of the study participants have not met anyone diagnosed with breast cancer. Based on the provided results, it seems that the main methods to detect breast cancer are breast self-examination as 43% of participants replied. Moreover, 44% of the study participants have no prior knowledge about any methods could be used to detect breast cancer. The results of the study revealed that study participants believed that the major risk factors of developing breast cancer are hereditary (28.6%) and medicines (26.8%). However, they believed unhealthy lifestyle is the less common risk factors reported among the study participants. When the study participants asked about the symptoms of breast cancer, the results appeared that 37.5% of them believed sensation of a lump in breast cancer and presence of nipple secretion (35.4%) are the main symptoms compared to 1.3% of participants thought inward turning of the nipple.

Table 5 indicates that study participations believed female when she reached puberty before aged 15 years increases the risk of breast cancer as 67.8% of the sample outlines. In addition, other risk factors were noticed is age of marriage. For instance, they thought females when got married before aged 24 years increases the risk of breast cancer. In addition, half of the study sample believed

Table 2. Knowledge about breast self-examination among women.

		N	%
Knowledge	Poor awareness	340	88.5
	Moderate awareness	44	11.5
	Good awareness	0	0.0
	Total	384	100.0

Table 3. Risk rates about breast cancer among women.

	N	%
Less risk factors	263	68.5
Moderate risk factors	94	24.5
High risk factors	27	7.0

Table 4. The study respondents on knowledge scale of breast cancer.

Knowledge Scale	Frequency	Percent
Have you heard about breast cancer?		
Yes	209	54.4
No	175	45.6
If yes, what are your sources of information about breast cancer?		
Books	91	23.7
Social media	148	38.5
Internet	77	20.1
Friends and relatives	21	5.5
Teachers	27	7.0
Doctors and nurses	20	5.2
Have you met or known a patient with breast cancer?		
yes	187	48.7
no	197	51.3
What are the methods of early detection of breast cancer that you know?		
I don't know any method	169	44.0
Breast self-examination	165	43.0
Clinical examination of the breast	23	6.0
Radiological examination for the breast (mammogram)	27	7.0
What are the risk factors for women developing breast cancer that you know of?		
Hereditary	110	28.6
Medicines	103	26.8
Exposure to radiation	28	7.3
old age	19	4.9
Unhealthy lifestyle	11	2.9
Childlessness	13	3.4
Puberty at an early age	14	3.6
Menopause at a late age	14	3.6
Obesity	27	7.0
Infection of family members with breast cancer	43	11.2
Other causes	2	0.5
What are the symptoms of breast cancer that you know?		
Sensation of a lump in the breast	144	37.5
Presence of nipple secretions	136	35.4
Nipple swelling	21	5.5
Ulceration of the breast	30	7.8
Inward turning of the nipple	6	1.6
Breast pain	5	1.3
Redness of the breast	9	2.3
Itching in the nipple	16	4.2
Having an armpit contract	8	2.1
Others	9	2.3

Table 5. The study respondents on risk factor of breast cancer.

Risk Factor	Frequency	Percent
How old were you when you reached puberty?		
9 - 12	151	39.3
12 - 15	148	38.5
15 - 18	38	9.9
15 - 21	47	12.2
How old were you when you got married?		
16 - 20	150	39.1
20 - 24	141	36.7
24 - 28	27	7.0
28 - 32	28	7.3
More than 32	38	9.9
How old were you when you got pregnant for the first time?		
16 - 20	148	38.5
20 - 24	138	35.9
24 - 28	19	4.9
28 - 32	34	8.9
More than 32	45	11.7
Number of pregnancies		
0	172	44.8
1 - 3	163	42.4
4 - 6	22	5.7
More than 6	27	7.0
The number of abortions		
0	175	45.6
1 - 3	148	38.5
4 - 6	40	10.4
More than 6	21	5.5
Number of children		
0	179	46.6
1 - 3	135	35.2
4 - 6	41	10.7
More than 6	29	7.6
Have you used pills or injections to prevent pregnancy?		
Yes	192	50.0
No	192	50.0
If the answer to the previous question is yes, how long did you use contraceptives?		
1 year	163	42.4
2 years	152	39.6
3 years	31	8.1
More than 3 years	38	9.9
Has anyone in your family had breast cancer?		
Yes	204	53.1
No	180	46.9

Continued

If the answer to the previous question is yes, what is the degree of her kinship to you?		
Sister	126	32.8
Mother	129	33.6
Grandmother	23	6.0
Aunt	77	20.1
Other	29	7.6
Do you do any physical activities to maintain your weight?		
Yes	202	52.6
No	182	47.4
If the answer to the previous question is yes, what are these activities?		
Walking	170	44.3
Jogging	156	40.6
Sports	21	5.5
Other	37	9.6
How often do you do this physical activity?		
Every day	146	38.0
Once a week	133	34.6
Once a month	44	11.5
Irregular	61	15.9
Do you smoke?		
Yes	162	42.2
No	183	47.7

using pills or injection could increase the risk of breast cancer. More than half of the study sample highlights positive family history increases the risk for breast cancer. This risk is accelerated when first-degree family relative diagnosed with breast cancer, as described in Table 5.

Table 6 shows that (61.7%) had poor practice and trends in the early diagnosis of breast cancer, and (33.9%) and (4.4%) had moderate and good practice respectively in the early diagnosis of breast cancer.

Table 7 shows the One-Sample Statistics according to the knowledge about breast self-examination, risk factors about breast cancer, trends and practices in early diagnosing of breast cancer, the highest mean was regarding the trends and practice (0.43). There was a positive significant statistical relationship regarding the knowledge about breast self-examination, risk factors about breast cancer, trends and practices in early diagnosing of breast cancer at P-value (0.00, 0.000, 0.00) respectively. Increasing knowledge in a positive way about breast cancer reduces the risk of cancer.

Table 8 shows the correlations between the knowledge about breast self-examination with trends and practices in early diagnosing of breast cancer, there were a positive significant statistical correlation between knowledge about breast self-examination with trends and practices in early diagnosing of breast

Table 6. Trends and practices in the early diagnosis of breast cancer.

	N	%
Poor Practice	237	61.7
Moderate Practice	130	33.9
Good Practice	17	4.4

Table 7. One-Sample statistics according to the knowledge about breast self examination, risk factors about breast cancer, trends and practices in early diagnosing of breast cancer.

	N	Mean	Std. Deviation	Std. Error Mean
Knowledge about breast self-examination among women	384	0.11	0.319	0.016
Risk about breast cancer among women	384	0.39	0.615	0.031
Trends and practices in the early diagnosis of breast cancer	384	0.43	0.578	0.029

One-Sample Test

	Test Value = 0				
	t	df	P-value	Mean Difference	95% Confidence Interval of the Difference
					Lower
Knowledge about breast self-examination among Women	7.040	383	0.000	0.115	0.08
Risk about breast cancer among Women	12.276	383	0.000	0.385	0.32
Trends and practices in the early diagnosis of breast cancer	14.479	383	0.000	0.427	0.37

Table 8. Correlations between the knowledge about breast self-examination with trends and practices in early diagnosing of breast cancer.

Knowledge about breast self-examination			Trends and practices in the early diagnosis of breast cancer
Knowledge about breast self-examination	Pearson Correlation	1	0.371**
	P-value		0.000
	N	384	384
Trends and practices in the early diagnosis of breast cancer	Pearson Correlation	0.371**	1
	P-value	0.000	
	N	384	384

cancer at P-value = 0.000.

6. Discussion

The results of the study provide important insights into the sociodemographic characteristics of our participants and their knowledge and practice regarding breast cancer. The majority of our participants were in the age range of 28-38 years, which is an important age group for breast cancer screening and early detection. However, the awareness and practice of breast self-examination and early diagnosis of breast cancer were found to be poor among our participants.

It is also noteworthy that a significant percentage of our participants had regular menstrual cycles and were married, which indicates that they may be at higher risk for breast cancer. However, the majority of them had less risk factors for breast cancer. This suggests that there is a need for targeted breast cancer education programs to increase awareness and knowledge among this population.

Furthermore, our study found that the level of education and income had no significant relationship with knowledge and practice related to breast cancer. This highlights the need for targeted education programs that are accessible and culturally appropriate for all socioeconomic groups. It is encouraging to note that there was a significant correlation between knowledge about breast self-examination and early diagnosis of breast cancer, which suggests that education and awareness programs can be effective in promoting early detection and diagnosis of breast cancer. However, further research is needed to identify the most effective methods for promoting breast cancer awareness and early detection among different populations.

In consistent to these finding few studies were found such as a study found that the knowledge about breast cancer and breast self-examination among Omani females was inadequate. Only 15.3% of the participants had ever performed breast self-examination. There was a significant association between education level and knowledge about breast cancer and breast self-examination. Health education programs targeting women in Oman are needed to improve breast cancer knowledge and promote early detection through breast self-examination [32]. As well as a systematic review found that the knowledge about breast cancer and its screening methods was low among women in Saudi Arabia. There were several misconceptions and myths related to breast cancer, such as the belief that it is contagious or caused by stress. The study also found that the utilization of breast cancer screening services was low among women in Saudi Arabia, with many women reporting fear and embarrassment as barriers to undergoing breast cancer screening. And a study found that the knowledge about breast cancer and its risk factors was generally low among female healthcare workers in China. However, the study found that healthcare workers who had received breast cancer education had significantly higher knowledge scores compared to those who had not received such education. The study also found

that many female healthcare workers in China had misconceptions about breast cancer, such as the belief that it is a rare disease or that it only affects older women. In addition to some inconsistent studies such as a study found that only 28.6% of female undergraduate students in Nigeria had adequate knowledge of breast self-examination (BSE). Attitude towards BSE was positive, but practice of BSE was low (14.3%). Factors such as age, marital status, and family history of breast cancer were found to be significantly associated with knowledge, attitude, and practice of BSE [33]. As well as a study found that knowledge was positively associated with breast cancer risk perception and screening behavior in the UK population. Those who were more knowledgeable about breast cancer were more likely to perceive themselves as being at higher risk of developing the disease, and to engage in recommended screening behaviors. And a study found that knowledge of breast cancer and BSE was generally poor among Yemeni women, with only 22.8% of participants having adequate knowledge. However, a positive attitude towards BSE was reported by 85.7% of participants, and 30.2% reported practicing BSE regularly. Factors such as education level, marital status, and having a family member with breast cancer were found to be significantly associated with knowledge, attitude, and practice of BSE [34].

In conclusion, our study provides important information about the sociodemographic characteristics and knowledge and practice related to breast cancer among a specific population. The findings highlight the need for targeted education programs that are culturally appropriate and accessible for all socioeconomic groups to improve early detection and diagnosis of breast cancer.

6.1. Strengths and Limitations of the Study

Strengths of the study include the large sample size, which increases the generalizability of the results. Additionally, the study covered a range of sociodemographic characteristics, breast cancer knowledge, risk factors, and practices, providing a comprehensive understanding of the topic.

However, studying has several limitations. First, the study relied on self-reported data, which may be subject to recall bias and social desirability bias. Second, the study was conducted in a specific geographical area, and the findings may not be generalizable to other populations. Third, the study did not consider factors such as cultural beliefs and health literacy, which may influence breast cancer knowledge, risk factors, and practices.

Overall, the study provides valuable insights into the breast cancer-related knowledge, risk factors, and practices among women in the study population, but future studies should address the limitations identified to increase the validity and reliability of the findings.

6.2. Conclusion

In conclusion, the study found that there were several sociodemographic characteristics associated with breast cancer knowledge and practice among the par-

ticipants. A majority of participants were aged between 28 - 38 years and had a regular menstrual cycle, while a small percentage of them had a collegiate degree and practiced exclusive breastfeeding for at least 6 months. The study also found that the participants had poor awareness and knowledge about breast self-examination and trends and practices in the early diagnosis of breast cancer. Furthermore, there was a significant relationship between knowledge about breast self-examination, risk factors for breast cancer, and trends and practices in early diagnosing of breast cancer. The study recommends increasing awareness campaigns on breast cancer and providing educational programs for women to improve their knowledge and practices related to early breast cancer detection.

6.3. Implications for Nursing

The study has important implications for nursing practice. The findings suggest that there is a need for more education and awareness programs for women regarding breast self-examination, risk factors for breast cancer, and early diagnosis of breast cancer. Nurses can play a vital role in educating and raising awareness among women about breast cancer, its risk factors, and early detection methods. They can provide individualized education sessions to women, and also develop group education sessions for communities to raise awareness about the importance of early diagnosis and treatment of breast cancer.

Additionally, nurses can work with other healthcare providers to ensure that women have access to breast cancer screening programs and resources. They can also collaborate with community organizations and stakeholders to develop community-based programs that focus on breast cancer awareness and education.

Overall, the study highlights the importance of nursing interventions in promoting breast cancer awareness, education, and early detection. By implementing these interventions, nurses can help reduce the burden of breast cancer and improve health outcomes for women.

6.4. Recommendations for Further Future

Firstly, future studies can focus on increasing the sample size and including a more diverse population to increase the generalizability of the findings. Additionally, researchers can use a randomized controlled trial design to test the effectiveness of educational interventions aimed at improving knowledge and practice related to breast cancer.

Secondly, qualitative studies can be conducted to explore the cultural and societal beliefs and practices that influence the knowledge and practices related to breast cancer among women. This information can be used to develop culturally sensitive and tailored interventions to improve breast cancer knowledge and practice.

Lastly, future studies can also explore the role of healthcare providers in promoting early detection and diagnosis of breast cancer. This can include investi-

gating the barriers that prevent healthcare providers from effectively educating and screening women for breast cancer and developing strategies to address these barriers.

Overall, the findings of this study highlight the need for improved education and awareness campaigns to promote breast cancer knowledge and practice among women. Future research can build upon these findings to develop effective interventions and strategies to improve breast cancer outcomes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Effect of Trimetazidine on Functional Capacity in Patient with Ischaemic Cardiomyopathy (TOFCAPI)

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Abstract

Objective: This study aimed to evaluate the efficacy of trimetazidine on exercise capacity via a six-minute walk test in patients with ischaemic cardiomyopathy and also evaluate the effect of trimetazidine on left ventricular function via echocardiography in the same population. **Methods:** This prospective observational study, conducted at the National Institute of Cardiovascular Diseases in Dhaka, Bangladesh, enrolled 200 patients with ischaemic cardiomyopathy and a depressed left ventricular ejection fraction (LVEF < 35%). We investigated the effects of modified-release trimetazidine on exercise capacity and left ventricular function in ischaemic cardiomyopathy patients with an LVEF less than 35%. The cohort, was divided into Group 1, which received modified-release trimetazidine alongside standard anti-ischaemic therapy and Group 2, which received standard therapy. Patients were subjected to a year-long study with follow-ups at the 1st and 6th months. Using SPSS software, statistical analysis was used to assess treatment-related effects and baseline comparability. **Results:** In this study (n = 200) of ischaemic cardiomyopathy patients, the mean age was 58 years, with 76% of the patients being male. All study subjects received GDMT (Guideline-Directed Medical Therapy) for angina and heart failure. Those who received the modified released form of trimetazidine developed lesions during the 1st and 2nd

follow-ups, during which the LVEF, LVIDd, and six-minute walk distance significantly improved ($p < 0.05$). There was a progressive improvement in functional status, which was statistically highly significant at the second follow-up. **Conclusion:** The findings of the present study demonstrated that the addition of modified-release trimetazidine to GDMT can improve exercise capacity and left ventricular function in patients with ischaemic cardiomyopathy.

Keywords

Bangladesh, Heart Failure, Exercise Capacity, Trimetazidine, Ischaemic Cardiomyopathy

1. Introduction

Exercise capacity is a more powerful predictor of mortality than other established risk factors for CVD [1] [2]. Exercise capacity is expressed in terms of metabolic equivalents (METs), which are common clinical measures of exercise tolerance. It has been found that each 1-MET increase in exercise capacity confers a 12% improvement in survival [1].

Myocardial energy metabolism may normalise in the early stages of heart failure, but as failure progresses, mitochondrial oxidative metabolism is reduced and glycolysis is increased with the downregulation of glucose and fatty acid oxidation [3]. Although there have been considerable advances in therapeutics, heart failure remains a leading cause of mortality and morbidity in developed countries and is becoming increasingly common in developing countries [4] [5]. Reducing free fatty acid (FFA) oxidation and, increasing glucose oxidation improve cardiac contraction and slow the progression of left ventricular (LV) failure [4]. Failure of the myocardium in heart failure appears to be caused to some degree by alterations in substrate metabolism [6]. Trimetazidine acts as a partial inhibitor of fatty acid oxidation and, in turn, stimulates glucose oxidation [5] [6] [7]. Improvements in LV systolic function with trimetazidine in heart failure patients, especially those with diabetes, have been reported in several studies [8]-[13].

The efficacy of trimetazidine has been well studied in numerous large-scale international clinical studies as well as RCTs. However, few small-scale studies have been performed on the Bangladeshi population. Therefore, it is of particular interest to study its efficacy on a large scale among the Bangladeshi population.

The aim of the present study was to evaluate the efficacy of trimetazidine on exercise capacity by a six-minute walk test in patients with ischaemic cardiomyopathy and to evaluate the effect of trimetazidine on left ventricular function by echocardiography in the same population.

2. Materials and Methods

2.1. Study Design

This study used a prospective observational method and was carried out at Dhaka's National Institute of Cardiovascular Diseases. The primary goals of the study were to assess the impact of modified-release trimetazidine on the capacity of patients suffering from ischaemic cardiomyopathy to exercise. The secondary objective was to evaluate the effect of trimetazidine on left ventricular function in patients with ischaemic cardiomyopathy.

2.2. Participant

Participants in this single-center study were diagnosed with ischaemic cardiomyopathy, which was defined by an echocardiogram-confirmed left ventricular ejection fraction (LVEF) of less than 35%. All patients were uenrolled after six months and treatment was administered for one year overall. Participants had to meet three criteria to be eligible: they had to have ischaemic cardiomyopathy, an LVEF of less than 35%, or at least one case of heart failure hospitalisation in the year before admission. Those with unstable angina, abrupt cardiac failure, chronic pulmonary or systemic illnesses, or renal insufficiency were excluded due to specific criteria.

Based on the findings of an echocardiogram, modifications in the electrocardiogram (ECG), symptoms, and results of coronary angiography (CAD), stable ischaemic cardiomyopathy was diagnosed. Over the course of the six months, a thorough screening process was used to enroll patients and those who met the eligibility requirements.

A single drug in the morning and one in the evening were the recommended dosages of modified-release trimetazidine, which was administered as part of the treatment. Throughout the course of the trial, this standardised strategy attempted to guarantee constant compliance with the treatment plan.

3. Procedures

The study procedures included a systematic approach to evaluate the effect of trimetazidine on patients' capacity to exercise and left ventricular function in cases of ischaemic cardiomyopathy. The participants were divided into two groups for comparative purposes. Group 2 received standard treatment combined with a control treatment, while Group 1 received regular therapy with modified-release trimetazidine. Throughout the trial, modified-release trimetazidine and substitute medication were given according to the recommended dosage.

3.1. Recruitment and Screening

Prospective participants were carefully screened over a six-month period using predetermined inclusion and exclusion criteria. After that, those who qualified were contacted to obtain their informed consent, guaranteeing that they fully

understood the study.

3.2. Baseline Assessments

Baseline assessments focused on confirming a left ventricular ejection fraction (LVEF) of less than 35%. Along with additional techniques, echocardiography was used in these evaluations. A comprehensive approach, taking into account the patient's symptoms, coronary angiography (CAD) results, electrocardiogram (ECG) findings, and echocardiography confirmation, led to the diagnosis of stable ischaemic cardiomyopathy.

3.3. Treatment Administration

Participants were given modified-release trimetazidine (Trimetazidinel®) according to standard recommendations. To ensure standarised and consistent treatment across the duration of the trial, the suggested maintenance included taking one medication in the morning and one in the evening.

3.4. Follow-Up Visits

Over the course of the six-month treatment plan, a number of routine follow-up appointments were planned. During these sessions, the patients' capacity to exercise was monitored, their left ventricular function was evaluated, and they were closely observed for any possible complications. The goal of this comprehensive approach was to record the constant modifications and reactions to trimetazidine.

3.5. Data Collection

For each participant, a comprehensive range of clinical and biochemical data was gathered, including BMI, blood pressure, demographic information, cardiovascular risk information, patient complaints, and biochemical criteria. The dataset included a variety of features, including the six-minute walk distance, NT-pro BNP levels, NYHA functional class, and echocardiographic measures such as LVEF, LVIDd, PASP, TAPSE, and MR grading. This all-inclusive methodology guarantees a comprehensive assessment of the effect of trimetazidine on ischaemic cardiomyopathy.

During the visit, standardised information collection methods were used to record data on safety parameters, exercise capacity, and left ventricular function. The utilisation of standardised forms and computerised records enabled thorough and uniform documentation, therefore improving the authenticity of the study data.

3.6. Outcome

The outcomes of the study were evaluated using two key objectives. Initially, the effect of trimetazidine on the ability of ischaemic cardiomyopathy patients to exercise was evaluated. Secondly, the effect of trimetazidine on the function of

the left ventricle in these patients was assessed.

This study included measurements such as six-minute walk distance and other important clinical indications for the primary goal of exercise capacity. The secondary objective was to evaluate left ventricular function via echocardiographic measurements such as the degree of mitral regurgitation (MR), pulmonary artery systolic pressure (PASP), tricuspid annular plane systolic excursion (TAPSE), left ventricular ejection fraction (LVEF), and left ventricular internal diameter in diastole (LVIDd).

Our study provides information on these results to better understand how well trimetazidine works to improve left ventricular function and exercise capacity in patients suffering from ischaemic cardiomyopathy. A detailed comprehension of the drug's effects on the population under study was made possible by the thorough evaluation of both primary and secondary objectives.

3.7. Statistical Analysis

The statistical analysis for this study was performed using SPSS software for Windows, version 25.0. Categorical variables were displayed as percentages, and continuous data were displayed as the mean ± SD. The student's t-test for independent group and Pearson's chi-square test for categorical variables were used to confirm baseline comparability between Group 1 (receiving modified-release trimetazidine) and Group 2 (receiving standard anti-ischaemic medication only). After the treatment, changes in the parameters were evaluated using repetitive measures analysis of variance (ANOVA), which enabled the analysis of within- and between-subject differences in the first and sixth months. A two-tailed p-value of 0.05 or less was considered to indicate statistical significance and provides an important basis for assessing how effectively trimetazidine works to improve the capacity for exercise and left ventricular function in ischaemic cardiomyopathy patients.

4. Results

The baseline characteristics (Table 1) of the study cohort, including differences between Group 1 (standard therapy with modified-release trimetazidine) and Group 2 (standard therapy alone), were not significantly different. Similarly, other variables such as BMI, vital signs, sex distribution, cardiovascular risk factor, and patient complaints showed no significant changes between the groups (all $p > 0.05$), the mean age of the participants was 58 ± 10.22 years, and there was a nonsignificant trend ($p = 0.052$) due to the small difference in years between Group 1 (56 ± 9.29 years) and Group 2 (60.2 ± 10.9 years).

The table shows the baseline characteristics of the study population. No significant difference was detected ($p > 0.05$).

Figure 1 shows the prevalence of angina severity by visually representing the distribution of Canadian Cardiovascular Society (CCS) anginal classes throughout the total study group. Significant changes were identified when examining

Table 1. Baseline characteristics of the study population.

	Overall (n = 200)	Group 1 (n = 106)	Group 2 (n = 94)	p-Value
Age	58 ± 10.22	56 ± 9.29	60.2 ± 10.9	0.052^{ns}
BMI (kg/m^2)	26.44 ± 4.74	26.71 ± 4.49	26.14 ± 5.04	0.552^{ns}
Pulse (min)	78.31 ± 6.91	78.26 ± 7.32	78.3 ± 6.5	0.947^{ns}
Systolic BP (mmHg)	120.7 ± 10.61	119.69 ± 14.28	121.85 ± 3.05	0.314^{ns}
Diastolic BP (mmHg)	81.53 ± 2.22	81.66 ± 2.51	81.38 ± 1.87	0.537^{ns}
Respiratory Rate (breaths/min)	19.58 ± 0.59	19.49 ± 0.61	19.7 ± 0.6	0.107^{ns}
Gender				
Male	152 (76%)	82 (77.4%)	70 (74.5%)	0.736^{ns}
Female	48 (24%)	24 (22.6%)	24 (25.5%)	
Cardiovascular Risk factors				
Hypertension	72 (36%)	40 (37.7%)	32 (34.1)	0.701^{ns}
Diabetes	86 (43%)	54 (50.9%)	32 (30.2%)	0.088^{ns}
Dyslipidemia	24 (12%)	16 (15.1%)	08 (8.5%)	0.312^{ns}
Smoking	32 (16%)	23 (21.7%)	09 (9.6%)	0.358^{ns}
Family History of IHD	25 (12.5%)	14 (13.2%)	11 (11.7%)	0.286^{ns}
Patient Complaints				
Palpitation	113 (56%)	96 (90.7%)	17 (18.1%)	0.286^{ns}
Syncope	07 (3.5%)	07 (6.6%)	00 (00%)	0.421^{ns}
Body Swelling	15 (7%)	13 (12.3%)	02 (2.1%)	0.286^{ns}
Shortness of Breath	174 (87%)	92 (86.8%)	82 (87.2%)	0.098^{ns}
H/O Cardiac Arrest	12 (6%)	09 (8.5%)	03 (3.2%)	0.241^{ns}
Biochemical Parameters				
RBS (mmol/l)	8.87 ± 4.53	9.36 ± 5.76	11.5 ± 30.7	0.615^{ns}
Hb (gm/dl)	11.84 ± 1.9	9.18 ± 11.22	8.7 ± 13.9	0.849^{ns}
Serum Ferritin (µg/l)	310.45 ± 436.7	311.23 ± 245.8	309.4 ± 425.5	0.291^{ns}
Serum creatinine (mg/dl)	1.34 ± 0.7	1.45 ± 0.9	2.3 ± 2.7	0.419^{ns}
TSH (mU/L)	3.25 ± 10.15	3.39 ± 7.23	1.2 ± 1.2	0.312^{ns}
Na^+ (mEq/L)	135.24 ± 99.8	145.7 ± 130.71	123.4 ± 43.47	0.267^{ns}
K^+ (mEq/L)	6.8 ± 13.07	5.3 ± 7.2	8.5 ± 17.4	0.218^{ns}
Cl^- (mEq/L)	87.9 ± 33.1	89.6 ± 32.5	86.2 ± 34.1	0.615^{ns}
NYHA Functional Class				
I	02 (1.0%)	00	02 (2.1%)	0.755^{ns}
II	06 (3%)	02 (1.9%)	04 (4.3%)	
III	54 (28%)	32 (30.1%)	22 (23.4%)	
IV	128 (69%)	98 (92.4%)	30 (31.8%)	

Continued

NT-pro BNP (pg/ml)	5351.08 ± 6034.5	4536.5 ± 6198.5	6269.6 ± 5771.74	0.153[ns]
Six minutes' walk distance (Feet)	135.6 ± 146.6	127.81 ± 131.44	144.36 ± 163.01	0.576[ns]
Echo				
LVEF (%)	30.25 ± 4.2	30.05 ± 4.1	30.5 ± 4.3	0.786[ns]
LVIDd (mm)	59.23 ± 10.07	59.3 ± 8.9	59.2 ± 11.3	0.687[ns]
PASP (mmHg)	29.00 ± 12.73	30.1 ± 3.7	29.5 ± 4.5	0.932[ns]
TAPSE (mm)	10.18 ± 2.88	11.3 ± 3.8	10.8 ± 3.2	0.291[ns]
MR (mild/moderate/severe)	3.00 ± 1.26	3.2 ± 1.6	2.9 ± 0.8	0.349[ns]

Ns: Not significant.

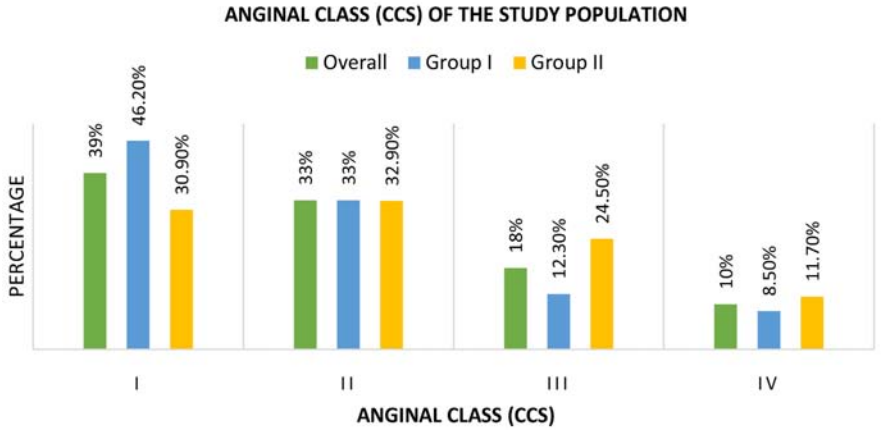

Figure 1. Anginal class (CCS) of the study population (n = 200).

certain treatment groups: In CCS I, II, III, and IV, Group 1 (standard therapy with modified-release trimetazidine) had percentages of 46.2%, 33%, 12.3%, and 8.5%, respectively. The distribution of patients in Group 2 (standard therapy only) was as follows: 30.9% for CCS I, 32.9% for CCS II, 24.9% for CCS III, and 11.7% for CCS IV.

Table 2 shows the background medications received by the study population. As shown in the above table, the majority of the participants were treated with aspirin (93%), diuretics (73.5%), and clopidogrel (48.5%). Then digoxin (43%), ß-blockers (24%), and ACE inhibitors (19.5%) were used. Fewer participants in the study population also received anticoagulants (8.5%). These numbers are also reflected in the groupwise distribution.

Table 3 shows significant improvements in the follow-up assessment. With improved exercise capacity, the six-minute walk distance improved significantly from 127.81 ± 131.44 feet during enrollment to 303.01 ± 125.6 feet at the second

Table 2. Background medication used by the study population (n = 200).

Drugs	Group: I (n = 106)	Group: II (n = 94)	Overall (n = 200)
Aspirin	102 (96.2%)	84 (89.4%)	186 (93%)
Clopidogrel	37 (34.9%)	60 (63.8%)	97 (48.5%)
Nitrate	52 (49.1%)	23 (24.5%)	75 (37.5%)
Beta Blocker	23 (21.7%)	26 (27.7%)	49 (24%)
ACE inhibitor	19 (17.9%)	20 (21.3%)	39 (19.5%)
Diuretics	85 (80.1%)	89 (94.7%)	174 (73.5%)
Digoxin	38 (35.9%)	48 (51.1%)	86 (43%)
Anticoagulants	12 (11.3%)	05 (5.3%)	17 (8.5%)

Table 3. Follow-up status of the study population (n = 200).

Group 1	During enrollment	1st follow up	2nd follow up		p-value
Six minutes' walk distance	127.81 ± 131.44	244.6 ± 142.7	303.01 ± 125.6		**<0.05^{s}**
LVEF	30.25 ± 4.2	38.2 ± 5.7	51.0 ± 6.7		**<0.05^{s}**
LVEDD	59.30 ± 8.92	53.09 ± 6.6	46.2 ± 4.95		**<0.05^{s}**
NT-pro BNP	4536.5 ± 6198.5	4671.3 ± 4875.3	3461.08 ± 4313.9		**<0.05^{s}**
		Group 2			
Six minutes' walk distance	144.36 ± 163.01	180.3 ± 135.7	212.97 ± 148.6		**<0.05^{s}**
LVEF	30.50 ± 10.26	34.7 ± 7.3	40.8 ± 7.03		**<0.05^{s}**
LVEDD	59.16 ± 11.33	58.7 ± 6.2	54.2 ± 6.2		**<0.05^{s}**
NT-pro BNP	6269.6 ± 5771.74	5619.5 ± 5671.2	5337.1 ± 5371.6		**0.544^{ns}**
Functional Class	**I**	**II**	**III**	**IV**	**p-Value**
1st follow-up					
Group 1	06 (5.7%)	30 (28.3%)	40 (37.7%)	30 (28.3%)	0.302^{ns}
Group 2	00 (0%)	22 (23.4%)	38 (40.4%)	34 (36.2%)	
Functional class					
2nd follow-up					
Group 1	20 (18.9%)	54 (50.9%)	22 (20.8%)	10 (9.4%)	**0.001^{s}**
Group 2	00 (0%)	08 (8.5%)	55 (58.5%)	31 (33%)	

Pair t-test and chi-square test was done to see the significance. **S:** Significant. **Ns:** Not significant.

follow-up ($p < 0.05$). Furthermore, a significant increase in the left ventricular ejection fraction (LVEF) was observed, increasing from 30.25% ± 4.2% to 51.0% ± 6.7% ($p < 0.05$), indicating improved heart efficiency. Moreover, there was a significant decrease in the left ventricular end-diastolic diameter (LVEDD) from 59.30 ± 8.92 mm to 46.2 ± 4.95 mm ($p < 0.05$), indicating positive structural changes. In Group 1, NT-pro BNP levels decreased significantly with time ($p < 0.05$). In Group 2, there were no statistically significant improvements ($p = 0.544$). With increased exercise capacity, the six-minute walk distance dramatically improved, from 144.36 ± 163.01 feet to 212.97 ± 148.6 feet ($p < 0.05$). Positive improvements in heart function and structure were further highlighted by the decrease in LVEDD from 59.16 ± 11.33 mm to 54.2 ± 6.2 mm ($p < 0.05$) and the increase in LVEF from 30.50 ± 10.26 to 40.8 ± 7.03 ($p < 0.05$). The levels of NT-pro BNP did not significantly decrease ($p = 0.56$).

Group 1 showed significant progress in the functional class assessment at the first follow-up, with 18.9% in Class I, 50.9% in Class II, 20.8% in Class III, and 9.4% in Class IV ($p = 0.001$). Among those classified 0% in Class I, 23.4% in Class II, 40.4% in Class III, and 36.2% in Class IV ($p = 0.302$), Group 2 showed smaller changes. At the second follow-up, the positive effects continued, with Group 2 demonstrating significant positive changes in functional classes and Group 1 maintaining improvement ($p = 0.001$).

As shown in Figure 2, Group 1 showed significant improvements in the Canadian Cardiovascular Society (CCS) anginal class analysis, with decreases in Class I patients (64.5% to 52.0%) and Class III patients (20.0% to 0.0%). Notably, a significant correlation ($p = 0.042$) was found between the therapy groups and anginal class modifications according to the Pearson chi-square test. These results indicate the intervention's possible effectiveness and its positive impact on the anginal condition.

5. Discussion

The findings of the present study demonstrated that the addition of modified-release trimetazidine to the GDMT can improve exercise capacity and left

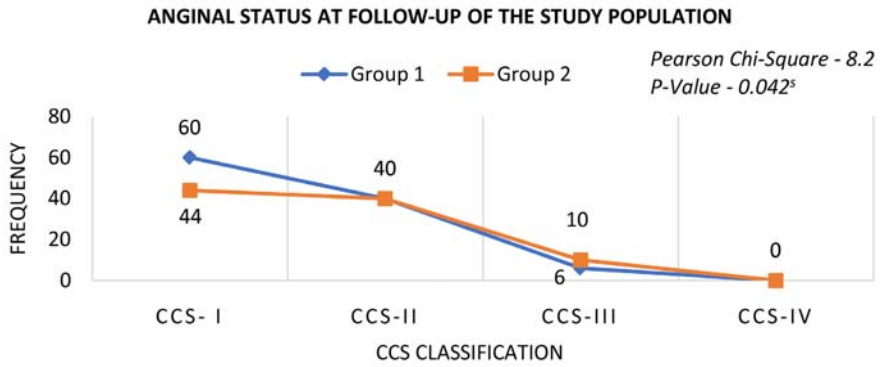

Figure 2. Anginal status of the study population during final follow-up (n = 200). s: Significant.

ventricular function in patients with ischaemic cardiomyopathy. In this study, patients with ischaemic cardiomyopathy were given a dose of 35 mg of modified-release trimetazidine twice a day to evaluate its effectiveness [1]. The advantage of this trimetazidine formulation is better patient compliance with therapy because of the lower frequency of drug administration compared to that of the conventional form. Trimetazidine increases cardiac contractility in individuals with ischaemic cardiomyopathy, which can be explained by the regulation of mitochondrial activity and increase in glycolytic adenosine triphosphate (ATP) generation [3] [4]. It is generally accepted that the myocardium needs a substantial amount of energy movement, with ATP functioning as the main source of energy. Beta-oxidation of free fatty acids and glucose breakdown are the two simultaneous mechanisms for energy delivery. The latter comprises glycolysis and lactate oxidation, which results in the degradation of pyruvate dehydrogenase to acetyl coenzyme A. The increase in myocardial contractility with trimetazidine treatment in patients with ischaemic cardiomyopathy can be explained by the regulation of mitochondrial function and by the increase in glycolytic adenosine triphosphate (ATP) synthesis [3] [4]. Under aerobic conditions, the myocardium generates energy predominantly by oxidizing free fatty acids (70% - 80%), with a smaller amount obtained from glycolysis (20% - 30%) [5]. The oxidation of glucose ensures the activity of ion pumps, Na^+/K^+ ATPase, and Ca^{2+} ATPase, which preserve the myocyte membrane potential and rapid transport of Ca^{2+} between subcellular compartments [5] [6]. The glycolytic and pyruvate pathways require less oxygen per mole of ATP produced than does free fatty acid oxidation [7]. The glucose-fatty acid cycle, described by Randle and colleagues in 1964, preserves the balance between available energy substrates [8]. Utilisation of glucose is controlled by the availability of insulin and also by competition with the free fatty acid pathway metabolites. Increased metabolism by the free fatty acid mechanism inhibits the glycolytic pathway, which may be unfavorable in situations of decreased oxygen delivery to the heart or under conditions such as stress, heart failure, and diabetes [9]. Trimetazidine selectively inhibits the long-chain 3-ketoacyl coenzyme. A thiolase is a key enzyme involved in the beta-oxidation of fatty acids. While reducing fatty acid oxidation, this compound stimulates glucose uptake and induces phosphorylation [3] [4]. In the present study, we assessed the impact of trimetazidine, when used with traditional antianginal medications on the functional ability of patients with ischaemic cardiomyopathy. Trimetazidine improved total functional capacity, as measured by the six-minute walk test. Our study showed that patients' functional capacity improved with time.

Greater improvement was observed after 6 months. The statistical analysis revealed highly significant values ($p = 0.032$ and 0.001, respectively). Compared to the meta-analysis results of Zhao *et al.*, which revealed a significant improvement in the six-minute walk test score following treatment with trimetazidine in IHD patients [2] [10], our results were comparable. According to Brottier and colleagues' pioneering study [11], the LVEF (determined by radionuclide angio-

graphy) increased by more than 9% compared with those in the placebo group in patients with ischaemic cardiomyopathy treated with trimetazidine for six months. In another study, Belardinelli and Purcaro (12) aimed to determine the effect of trimetazidine on LVEF by echocardiography in 38 patients with ischaemic cardiomyopathy. The resting LVEF in the trimetazidine-treated group increased from 33.1% ± 4.5% to 39.5% ± 5.9% (p = 0.001). On the other hand, our study showed that over the course of time, the left ventricular systolic function (analysed by echocardiography) also improved significantly, indicated by the decrease in the left ventricular end-diastolic diameter with time (53 mm and 48 mm) (p = 0.001). Another parameter used to assess systolic function was the LVEF (also measured by echocardiography). Additionally, the LVEF increased significantly in the trimetazidine-treated group of patients (Group 1). More improvement was observed in the second or last follow-up than in the first one after 6 months (38% and 51%, respectively). The statistical analysis showed highly significant values (p = 0.008 and 0.000, respectively). We also detected an improvement in the functional capacity of our patients by analysing their NYHA class, which showed a definite and statistically significant improvement in functional class in the trimetazidine-treated group (p = 0.001). In a meta-analysis performed by Gao *et al.*, seven of the included studies reported data compared to conventional therapy [13]. Both the NYHA and CCS classifications showed significant improvement. Additionally, in the subgroup analysis, the patients in Group 1 (the trimetazidine-treated group) also experienced significant improvements in terms of the LVEDD, LVEF, and the six-minute walk test.

In addition to improving the LVEF, trimetazidine can also improve arrhythmia by reducing heart rate variability [14] [15]. In our study, the analysis of demographic data such as age, sex, BMI, pulse, and systolic and diastolic blood pressure did not yield any statistically significant differences among the groups. Previously, all the other studies using trimetazidine rather than the standard anti-ischaemic drugs could not yield any statistical significance for their study population. We also did not find any differences from a demographic point of view. This is likely due to the similar baseline characteristics of the enrolled study population. From a risk factor analysis and laboratory parameters point of view, our study yields similar statistically insignificant results, which are comparable to those all-other studies and meta-analyses regarding trimetazidine. The obtained data support the therapeutic importance of metabolic treatment with the modified-release form of trimetazidine in patients with LV dysfunction and ischaemic cardiomyopathy. An improvement in LV function data indicate that the addition of trimetazidine to conventional therapy may lead to functional improvement in patients with ischaemic cardiomyopathy. The beneficial effect of treatment with trimetazidine was also shown by an improvement in exercise tolerance in these patients.

6. Limitations

The study team also confers some limitations on their study. They are:

- This was a single-center study. To make the findings more representative of the population, the study team would like to perform a multicenter study of this patient cohort with the molecule.
- The duration of the study was also small. If this could be done for a long time, the study could also yield a strong outcome.
- Moreover, the study population was small. Therefore, to ensure comprehensive results, a large study population is needed.
- Moreover, there has been no head-to-head analysis of the other conventional drugs used in ischaemic for treating cardiomyopathy to prove the superiority of these molecules over the other drugs.
- Complications like arrhythmia in this special group of patients were not included in this study to determine their effect.

7. Conclusion

Our study determined that the addition of modified-release trimetazidine to GDMT can improve exercise capacity and left ventricular function in patients with ischaemic cardiomyopathy. At follow-up, both groups showed significant improvements in cardiac indices and exercise capacity. Particularly in functional class assessments, Group 1, which was administered trimetazidine, showed significant improvements. These results are encouraging and should be further studied for validation and greater significance in the treatment of CVD.

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Conflicts of Interest

The authors of this study declare that they have no further financial interests, links, or affiliations with any individuals, organisations, or entities that could have compromised the impartiality and integrity of the research. The study follows ethical guidelines, and the authors confirm to the truth and transparency of the data they have provided.

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The Value of Excipients and the Required Understanding of the Biological System in Product Development: An Impactful Example of Curaderm, a Topical Skin Cancer Treatment

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Abstract

The incidences of nonmelanoma skin cancer are increasing worldwide, and the ongoing war on its treatment necessitates the development of effective and non-invasive methods. Through basic and clinical research, non-invasive treatments like Curaderm have been developed, leading to improved quality of life for patients. Excipients, previously considered inactive ingredients, play a crucial role in enhancing the performance of topical formulations. The development of Curaderm emphasizes the importance of understanding the interactions between active ingredients, excipients, and the biological system to create effective and affordable pharmaceutical formulations. The systematic approach taken in the development of Curaderm, starting from the observation of the anticancer activity of natural solasodine glycosides and progressing through toxicological and efficacy studies in cell culture, animals, and humans, has provided insights into the pharmacokinetics and pharmacodynamics of solasodine glycosides. It is crucial to determine these pharmacological parameters within the skin's biological system for maximal effectiveness and cost-effectiveness of a skin cancer treatment. Curaderm, as a topical treatment for nonmelanoma skin cancer, offers benefits beyond those obtained from other topical treatments, providing hope for improved quality of life for patients.

Keywords

Curaderm, BEC, Solasodine Glycosides, Solamargine, Apoptosis, Skin Cancer, Actinic Keratosis, Keratoacanthoma, Basal Cell Carcinoma, Squamous Cell Carcinoma

1. Introduction

In 1755 Jacques Daviel, a French surgeon was the first to describe the surgical removal of a skin cancer then known as a rodent ulcer, now known as a basal cell carcinoma (BCC). Since then, surgical resection has been the mainstay course of treatment for skin neoplasms.

Initially, surgical resection of skin cancers encountered high rates of recurrences of the treated skin cancers. As time progressed, the technology of surgical resection, including Mohs surgery of skin cancers improved, resulting in lower rates of recurrences.

Similar transitional phenomena occurred with cosmetic outcomes after surgical interventions. Presently, skin grafting or flaps are often necessary to improve the cosmetic outcome resulting in costly procedures.

Nevertheless, over the decades, surgical resections have improved the morbidity and mortality of people with skin cancers. However, remaining disadvantages of surgery include the incomplete resection of the tumor growth, poor postoperative quality of life, limited cosmetic results, scarring, and costliness.

2. Rising Rates of Skin Cancer Requires New Treatment Methods

The escalating rates of nonmelanoma skin cancer (NMSC) worldwide necessitate the development of non-invasive treatment methods. Curaderm represents one such approach, offering an alternative to surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapy.

2.1. Curaderm

This communication discusses the development of Curaderm, a topical formulation used for the treatment of NMSCs. Curaderm utilizes active anticancer components called BEC derived from Solanum plant extracts.

2.1.1. BEC

BEC Denotes the Initials of the Inventor of the Glycoalkaloid Technology and is a mixture of plant glycoalkaloids from the Solanaceae family. The Solanaceae, also known as the potato or deadly nightshade family is one of humankind's most utilized and important plant families. It contains some of the worlds most important food plants, such as the potato, tomato, and eggplant. BEC glycoalkaloids, specifically solasodine glycosides, are known for their biological activity and have been studied for their potential therapeutic effects in skin cancers.

2.1.2. Aglycone Solasodine

Solasodine, the aglycone of solasodine glycosides, is employed as a hormone precursor of corticosteroids, anabolic steroids, and antifertility drugs.

Solasodine has two chemical names Spirosol-5-en-3 beta-ol and Solasod-5-en-3 beta-ol. It also goes by other synonyms such as Solancarpidine, Solanidine-s, and Purapuridine. **Figure 1** shows the chemical structure of solasodine.

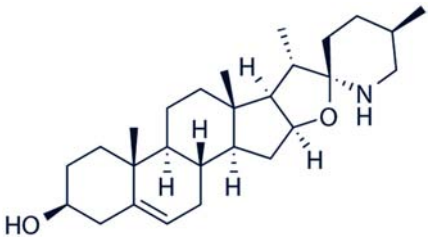

Figure 1. Chemical structure of Solasodine. Formal Name is (3beta, 22alpha, 25R)-spirosol-5-en-3-ol. Molecular Formula is C27H43NO2. Molecular mass is 414 [1].

2.1.3. Sugar Moieties of BEC Glycosides

In Solanum plants, solasodine is found as BEC, sugar(s) bound solasodine, consisting of monoglycosides, diglycosides, triglycosides, and tetraglycosides. The sugar moieties of the BEC glycosides are shown in **Table 1**.

2.2. Anticancer Effects of BEC

BEC is a natural drug that was first reported in 1987 to have remarkable anticancer effects in cell culture, animals, and humans [1] [2] [3]. The initial findings sparked interest and led to further investigations into the potential of BEC and its individual components as antineoplastic (anti-cancer) agents.

Over the years, numerous studies and experiments have been conducted to explore the efficacy and mechanisms of BEC in combating cancer. These investigations have demonstrated promising results, positioning BEC as a first-in-class natural drug with significant potential in the field of oncology [4]-[26].

The development of BEC as an antineoplastic agent has paved the way for a new family of drugs.

Figure 2 illustrates the rapid advancements and progress made in the understanding and utilization of BEC and its individual components for cancer treatment.

This communication discusses the development of Curaderm, a topical formulation used for the treatment of NMSCs. Curaderm utilizes the active anticancer BEC. The goal of this development was to create a treatment that is highly effective, safe, affordable, and provides excellent cosmetic outcomes.

When developing a pharmaceutical formulation, several factors must be considered to ensure its effectiveness, safety, reliability, and affordability. The formulation process consists of multiple stages, and the final product's quality is determined by the interactions among these stages. This includes the active pharmaceutical ingredient (API), valuable excipients (inactive ingredients), their interactions with the biological system, and the manufacturing procedure. Each component plays a crucial role in creating a beneficial medicinal product.

Curaderm's active ingredient, BEC, has been found to be effective against skin cancers at very low concentrations. However, to optimize its efficacy, it requires the cooperation of other essential ingredients present in the formulation. These ingredients work synergistically to enhance the overall effectiveness of the treatment.

Table 1. Sugar moiety of solasodine glycosides known as BEC

Glycosides	Sugar Moiety
γ-solamargine	Glucose $\beta(1 \rightarrow 3)$ – R
β_1-solamargine	Rhamnose $\alpha(1 \rightarrow 4)$ – Glucose $\beta(1 \rightarrow 3)$ – R
β_2-solamargine	Rhamnose $\alpha(1 \rightarrow 2)$ – Glucose $\beta(1 \rightarrow 3)$ – R
α-solamargine	Rhamnose $\alpha(1 \rightarrow 2)$ Rhamnose $\alpha(1 \rightarrow 4)$ > Glucose $\beta(1 \rightarrow 3)$ – R
γ-solasonine	Galactose $\beta(1 \rightarrow 3)$ – R
β_1-solasonine	Glucose $\beta(1 \rightarrow 3)$ – Galactose $\beta(1 \rightarrow 3)$ – R
β_2-solasonine	Rhamnose $\alpha(1 \rightarrow 2)$ – Galactose $\beta(1 \rightarrow 3)$ – R
α-solasonine	Rhamnose $\alpha(1 \rightarrow 2)$ Glucose $\beta(1 \rightarrow 3)$ > Galactose $\beta(1 \rightarrow 3)$ – R

R = Solasodine. BEC is composed of approximately 33% α-solamargine, 33% α-solasonine and 34% of β_1, β_2, γ solamargine and β_1, β_2, γ solasonine.

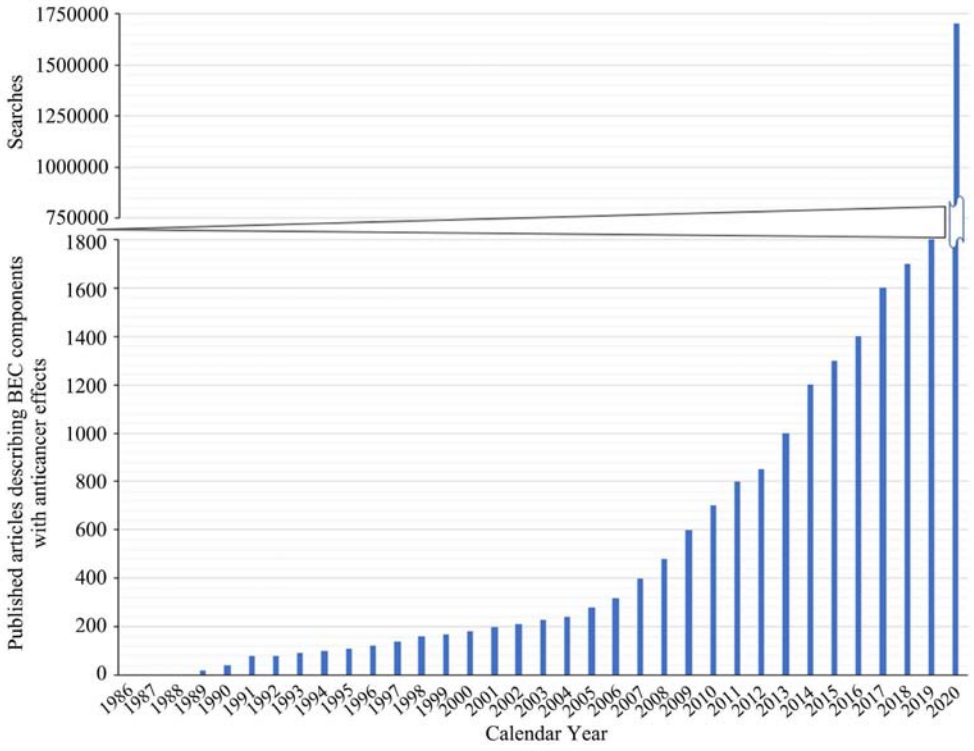

Figure 2. Importance of BEC and its components.

Since it was first reported that BEC had anticancer properties in 1987, there has been considerable interest in BEC and its components. In 2020, more than 1800 independently published articles describing the anticancer properties have been documented. In addition, there has been enormous scientific interest in BEC and its components. In the year 2020, more than 1.7 million searches of

these compounds have been reported.

In addition to efficacy, the formulation of Curaderm also focuses on safety. By carefully selecting excipients and ensuring their compatibility with the active ingredient and the biological system, the formulation aims to minimize potential adverse effects and maximize patient safety.

Cosmetic outcomes are other important considerations when treating skin cancers. Surgical interventions often require additional procedures like skin grafting or flaps to improve cosmetic results, which can be costly. Curaderm, on the other hand, aims to provide excellent cosmetic outcomes without the need for invasive procedures, thus reducing the stress and financial burden on patients.

Moreover, the escalating rates of NMSC worldwide necessitate the development of non-invasive treatment methods. Curaderm represents one such approach, offering an alternative to surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapy.

By highlighting the development of Curaderm and its unique properties, this communication emphasizes the importance of considering the biological and pharmacological systems together with the interactions between active ingredients and excipients in the formulation of pharmaceutical products. It also underscores the need for treatments that are effective, safe, affordable, and provide favourable cosmetic outcomes, ultimately improving the quality of life for individuals with skin cancer.

The mechanism of action of BEC in Curaderm involves its binding to specific mutant receptors located on the surface of cancer cells. This binding triggers a series of events within the cancer cell, leading to apoptosis or programmed cell death. The specificity of this mode of action makes it an attractive option for treating skin cancer, as it can selectively target cancer cells while minimizing damage to healthy cells.

Skin cancer is a significant global health issue, with increasing incidence, morbidity, and mortality rates. The two main types of skin cancer are melanoma, arising from dysfunctional melanocytes, and NMSC, which includes BCC and squamous cell carcinoma (SCC). In 2012, the United States reported 5.4 million new cases of NMSCs.

Skin cancer not only poses a burden on individuals' health but also has substantial psychosocial effects and requires significant investment in its treatment. The annual cost of treating nonmelanoma skin cancer in the U.S.A. is estimated at $4.8 billion. Conventional therapies for skin cancer have both advantages and drawbacks, and currently available commercial treatments do not adequately address the requirements for controlling this disease.

3. Results

The development and implementation of Curaderm as a treatment for skin cancer involves several steps. Firstly, extensive preclinical research and laboratory studies are conducted to understand the safety and efficacy of BEC in combating

skin cancer. These studies evaluate the effects of BEC on cancer cell lines and animal models.

Once preclinical studies demonstrate promising results, clinical trials are conducted to assess the effectiveness of Curaderm in human subjects. These trials involve recruiting patients with skin cancer and administering Curaderm as a topical cream according to specific protocols. The patients' response to treatment is monitored, and the safety and efficacy of Curaderm are evaluated.

If the results from clinical trials are positive, regulatory authorities review the data to determine whether Curaderm can be approved for commercial use. This involves assessing the product's safety, effectiveness, and quality. If approved, Curaderm can be made available to healthcare professionals and patients for the treatment of skin cancer.

It is important to note that the information provided here is a general overview and not a comprehensive guide to the conceptualization and implementation of Curaderm. The actual development process involves additional steps, such as formulation optimization, manufacturing scale-up, and post-marketing surveillance. Additionally, the specific regulations and requirements may vary depending on the country or region where Curaderm is being developed and marketed.

Clinical trials have been conducted to explore the use of BEC in the treatment of various types of skin cancers, including BCC and SCC. BEC exerts its effects by selectively targeting cancer cells while sparing healthy cells. It induces apoptosis (the process of programmed cell death) in cancer cells and has demonstrated anti-tumor activity in preclinical studies.

Clinical trials are conducted to assess the potential benefits and risks associated with a particular intervention or treatment approach.

Phase 1: Clinical Trial

The Phase I clinical trial investigated the use of varying concentrations of BEC (BEC01) in a cetomacrogol cream formulation for the treatment of actinic keratosis (AK), keratoacanthomas (KA), BCC, and SCC. The trial aimed to determine the tolerability, safety, and dose levels of BEC and evaluate its anticancer activity.

The study found that the BEC cream formulations at dose escalation concentrations ranging from 1% to 50% were well tolerated by the patients. No significant clinical or histological reactions were observed in normal skin treated with the BEC formulation. This indicates that the cream formulation was safe for use on the skin [2] [10].

Subjective observations suggested that a concentration of 10% BEC in the cream formulation was effective in treating the skin lesions. Therefore, a controlled clinical trial was conducted using a formulation called BEC02, which contained 10% BEC and 10% dimethyl sulfoxide (DMSO) in a cetomacrogol cream base [10].

In the controlled trial, over 90% of the NMSC lesions were successfully re-

moved by BEC therapy. The diagnoses of the lesions before and after treatment were confirmed through histological studies of standard biopsy specimens. The BEC treatment induced apoptosis (programmed cell death) in the skin tumor cells, similar to the effects observed in cell culture studies with BEC-treated cancer cells.

Some patients experienced transient itching and burning around the treated lesions, but these side effects were generally mild. Importantly, there were no recurrences of the treated lesions during the follow-up period of at least three years. This suggests that the BEC cream formulation was effective in permanently removing the lesions and preventing their recurrence.

Overall, the Phase I trial demonstrated that BEC cream formulations, particularly the 10% BEC formulation (BEC02), were well-tolerated and showed anticancer activity in patients with AK, KA, BCC, and SCC. The results supported further investigation and potential use of BEC as a treatment option for these skin lesions.

Phase I studies showed that a concentration of 10% BEC (10,000 mg BEC/L cream) was highly effective in regressing skin cancers. However, this concentration was deemed too costly for practical use as a skin cancer treatment. It was also observed that the efficacy of BEC depended not only on the quantity used but also on the composition of the formulation.

Concurrently with the phase 1 clinical studies, it was established with in vitro cell culture studies that as little as 6 to 10 micrograms of BEC/mL (6 to 10 mg BEC/L) were able to kill cancer cells [22]-[28]. Similarly, experiments on mice with Sarcoma 180 showed that a concentration of 8 mg/kg body weight of BEC was able to cure the cancer [4] [9] [29] [30]. Toxicity studies at these concentrations of BEC demonstrated high safety profiles.

Considering these findings, it was hypothesized that the bioavailability of BEC played a significant role in its effectiveness against cancer cells. In an aqueous environment where BEC was in direct contact with cancer cells, such as in the peritoneal cavity or cell culture media, approximately 10 mg BEC/L was sufficient to kill cancer cells. This concentration was much lower than the concentration used to treat *in vivo* skin cancer in Phase I trials (100,000 mg BEC/L cream), indicating a stark contrast.

The difference in bioavailability was believed to be the reason for this contrast. When treating *in vivo* skin cancer, BEC had low bioavailability with anchored cancer cells, whereas in vitro cell culture studies and intraperitoneal aqueous conditions allowed for direct contact between BEC and "swimming" cancer cells, leading to higher effectiveness at lower concentrations.

Improving the bioavailability of anticancer agents in skin cancers poses several challenges due to the skin's natural barriers and the presence of tumor cells. Some strategies considered to enhance drug delivery and improve the efficacy of topical treatments were:

1) Penetration enhancers: Various penetration enhancers can be used to

overcome the barrier function of the stratum corneum. These substances can temporarily disrupt the lipid structure of the skin, allowing better penetration of drugs. Examples of penetration enhancers include surfactants, liposomes, and chemical permeation enhancers such as DMSO or ethanol. Care should be taken to ensure the safety and compatibility of these enhancers with the specific anticancer agent being used.

2) Nanocarriers: Utilizing nanotechnology-based delivery systems, such as liposomes, nanoparticles, or micelles, can enhance drug penetration into the skin and improve its bioavailability. These carriers can encapsulate the drug and facilitate its transport through the skin layers, providing controlled and targeted release at the tumor site.

3) Physical methods: Techniques like iontophoresis, sonophoresis, and microneedles can enhance drug permeation through the skin. Iontophoresis involves the use of an electric current to drive charged drug molecules across the skin. Sonophoresis uses low-frequency ultrasound to disrupt the stratum corneum and enhance drug delivery. Microneedles create temporary channels in the skin, allowing drugs to pass through more easily.

4) Chemical modifications: Modifying the drug molecule itself can improve its permeability through the skin. Pro-drug approaches involve modifying the drug structure to enhance its lipophilicity or decrease its molecular size, making it easier to penetrate the skin. This modification can be reversed by enzymatic or chemical processes at the target site, releasing the active drug.

5) Combination therapies: Using a combination of different strategies can synergistically improve drug delivery to skin cancer cells. For example, combining penetration enhancers with nanocarriers or physical methods can further enhance drug penetration and target tumor cells more effectively.

6) Targeted therapies: Developing drugs specifically designed to target the molecular characteristics of skin cancer cells can improve their bioavailability and minimize adverse effects on healthy skin. Targeting tumor-specific receptors, enzymes, or signalling pathways can enhance drug uptake by cancer cells and increase therapeutic efficacy.

It is important to note that the development and application of these strategies should be supported by rigorous scientific research and preclinical/clinical studies to ensure their safety and effectiveness in treating skin cancers.

With BEC, it was decided to concentrate on penetration enhancers and targeted therapies for the effective treatment of skin cancers.

CONCEPTUALISATION TO IMPLEMENTATION OF CURADERM WITH EMPHASIS ON MAXIMAL BIOAVAILABILITY OF BEC WITH SKIN CANCER CELLS

Challenges with skin barriers

The outermost epidermal layers of the skin, constituting the stratum corneum, are the main cutaneous barriers and influence the uptake of anticancer agents into target cells, consequently affecting the response to topical treatments. The

stratum corneum in the human skin is composed of approximately 15 - 30 corneocyte cell layers that provide a thickness of approximately 10 - 20 micrometers. Several types of lipids such as phospholipids and cholesterols together with metabolic triglycerides and non-esterified fatty acids form a complex network with corneocytes that can absorb limited amounts of water and control the penetration of various sizes and types of molecules through the skin.

In general, skin cancer has a thicker keratin layer with increased lipid content resulting in an increased barrier to the passive transport of macromolecules.

In addition, with skin cancer, tumor cells can extend throughout the epidermis and dermis. Another biological barrier is created by the tumor itself affecting deeper located skin cancer cells. The interstitial space between the tumor cells becomes dense and is composed of collagen, proteins, elastic fibres, and glycosaminoglycans resulting in increased barriers for the transport of drugs to their target.

Cohesion of epidermal cells in the skin depends on desmosomes, which contain many specialised protein complexes, including desmogleins. Desmoglein is a catherin-like adhesion molecule to maintain tissue integrity and facilitates cell-cell communication.

Cadherin is a transmembrane protein that binds with other cadherins to form junctions known as desmosomes between cells. Desmogleins are expressed everywhere in the skin epidermis, but mainly they are expressed in the superficial upper layers of the skin epidermis. These desmogleins play a key role in the formation of desmosomes that join cells to one another.

Overcoming the Barrier

Excipients were at one time considered to be "inactive" ingredients but now they are understood to be able to serve as "key determinants of dosage form performance". In the context of a cream composition, an excipient is a natural or synthetic substance formulated alongside the active ingredient of the medication to give a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug interaction with targeted diseased state, solubility and stability of the medication over the expected shelf life.

Salicylic acid is a lipid-soluble organic acid that extracts desmosomal proteins including desmogleins resulting in the loss of the cohesion of epidermal cells. Being a lipophilic agent, salicylic acid also removes intercellular lipids such as ceramides, which are linked covalently to the cornified envelope surrounding epithelial cells. Thus, salicylic acid is known to affect the skin by loosening and breaking apart desmosomes (attachments between cells in the outer layers of the skin). In this context, salicylic acid is a desmolytic agent, because its mechanism of action works by disrupting cellular junctions. Salicylic acid can lead to alterations in the underlying dermal tissue without directly wounding the skin. Depending on the concentration, salicylic acid also dissolves the keratin plugs and regulates the skin cells.

Consequently, the combined effects of salicylic acid result in loosening of skin cells, including skin cancer cells, and are akin to cells in cell culture media whe-

reby the bioavailability of BEC to such exposed skin cells are vastly improved.

Similarly, but by a different mechanism of action, urea breaks hydrogen bonds among biopolymers leading to reversible structural destabilization of epidermal proteins claudin, desmoglein, filaggrin and proteases of the intercellular matrix of the cells of the skin. Urea exerts its effect directly, by binding to the proteins, or indirectly, by altering the solvent environment. Urea binds to, and stabilizes, the denatured state, thereby favouring unfolding of the protein. This improves the bioavailability of BEC with skin cells, approaching cell culture and intraperitoneal conditions.

Salicylic acid and urea at appropriate concentrations can overcome biological barriers and can improve targeted drug delivery to the tumor sites. This enables the use of lower doses of BEC with increased treatment efficacy and decreased number and/or severity of side effects.

Salicylic acid also has another beneficial effect, its presence in the formulation results in acidic aqueous conditions with low pH that enhances the solubility of BEC. In accordance with the Quality-by-Design (QbD) approach, it was predictable that the presence of salicylic acid and urea in a topical cream formulation would pose certain challenges such as stability of the cream [31] and that this had to be addressed.

To address the challenges posed by the presence of salicylic acid and urea in a topical cream formulation, several strategies were employed:

1) Selection of appropriate excipients: Excipients play a crucial role in stabilizing the formulation and maintaining its physical and chemical properties. Careful selection of excipients that are compatible with salicylic acid and urea is essential. Excipients such as emulsifiers, thickeners, and stabilizers can help improve the stability of the cream.

2) pH adjustment: As described, salicylic acid contributes to the acidic aqueous conditions of the formulation. The pH of the cream should be carefully controlled and optimized to enhance the solubility of the active ingredient (BEC) without compromising the stability of the formulation. Buffering agents can be added to maintain the desired pH range.

3) Formulation design: The formulation was designed to ensure proper dispersion and distribution of salicylic acid, urea, and other ingredients throughout the cream. Homogeneous distribution of the active ingredients helped to ensure consistent performance and efficacy of the product.

4) Compatibility testing: Compatibility studies were conducted to assess the physical and chemical interactions between salicylic acid, urea, and other formulation components. This helped to identify any potential incompatibilities or stability issues that arose during storage or use.

5) Stability testing: The stability of the cream formulation was evaluated under various storage conditions, including temperature, light, and humidity. Accelerated stability studies provided insights into the long-term stability of the cream and helped determine its shelf life.

6) Packaging considerations: The selection of appropriate packaging materials is crucial to prevent interactions between the formulation and the container. Packaging should be resistant to moisture, light, and air to maintain the stability of the cream over its intended shelf life.

7) Manufacturing process optimization: The manufacturing process was optimized to ensure uniform mixing and dispersion of ingredients. Proper temperature control and mixing techniques were employed to minimize degradation or loss of active ingredients.

8) Quality control measures: Regular quality control testing was performed to monitor the stability and consistency of the cream formulation. This included testing for pH, viscosity, active ingredient content, and microbial testing.

By implementing these strategies, the challenges associated with the presence of salicylic acid and urea in a topical cream formulation were effectively addressed.

Natural Drug Products Limitations

Limitations with natural products include variation in preparation methods and therefore also chemical composition, dosage determination and adjustment, and the suitable route of administration. These limitations were addressed and solved by studying the anticancer contribution of the individual components of BEC.

It was previously reported that the contribution of anticancer activities in BEC is 86% for solamargine, 9% for solasonine and 5% for monoglycosides and diglycosides of solasodine. Solamargine-quantified BEC with measured IC_{50} (effective doses) values in various human cancer cell lines are identical to pure solamargine. It was subsequently reported that topical cream formulations with identical excipients containing 0.02 mg purified isolated solamargine per 1 mL cream had comparable therapeutic outcomes as 0.05 mg BEC (containing 0.02 mg solamargine) per 1 mL cream [32].

Exploration of Low Concentrations of BEC with Salicylic Acid and Urea

A wide variety of components in cream formulations were investigated to determine their suitability for improving the bioavailability of BEC with skin cancer cells. Ultimately, it was possible to prepare a cream formulation Curaderm that contained set concentrations of salicylic acid, urea and BEC to treat skin cancer effectively and safely with very low concentrations of BEC.

Phase II: Clinical Trials

Phase II clinical trials were undertaken with the designated Curaderm topical cream formulation for the treatment of premalignant and malignant skin cancers in humans. These Phase II clinical trials showed that Curaderm was effective for the treatment of AKs, KAs, BCCs and SCCs of the skin in humans [10].

However, during these clinical trials two flaws in the cream formulation were identified:

- Heath instability of the cream formulation integrity even at room temperature; and
- Degradation of the glycoalkaloids in the cream formulation.

These flaws were further explored and were eventually overcome by adding xanthan gum and lactic acid to the cream formulation. Xanthan gum stabilized the emulsion of the cream and lactic acid added to the keratolytic action and prevented the degradation of the glycoalkaloids in the cream formulation [31]. This novel topical cream formulation with appropriate excipients resulted in a substantially stable, efficacious cream formulation with a shelf life of 4 years when used clinically [3]. With this in place, embarkation on Phase III clinical trials ensued.

Phase III Clinical Trials

After addressing the flaws in the cream formulation and achieving stability, Phase III clinical trials were initiated to further evaluate the efficacy and safety of the Curaderm topical cream formulation for the treatment of premalignant and malignant skin cancers in humans. These trials involved a larger number of participants and were conducted in multiple centres to gather more comprehensive data.

The Phase III clinical trials followed rigorous protocols and included a control group for comparison. Participants with various types of skin cancers, such as AKs, KAs, BCCs, and SCCs, were recruited. The cream formulation was applied topically to the affected areas according to the specified dosage and administration instructions.

During the Phase III trials, the efficacy of Curaderm was evaluated based on various factors, including tumor regression, reduction in lesion size, prevention of tumor recurrence, and overall patient satisfaction. Safety assessments were also conducted to monitor for any adverse effects or complications associated with the cream formulation.

The results of the Phase III clinical trials provided crucial evidence regarding the effectiveness of Curaderm for the treatment of skin cancers. The cream formulation demonstrated very high efficacy in inducing tumor regression, reducing lesion size, and preventing tumor recurrence. Additionally, the safety profile of the cream formulation was found to be acceptable, with minimal adverse effects reported.

These trials involved both uncontrolled and controlled double-blind, randomized, vehicle-controlled, parallel group, multicentre studies [33]-[42] showing highly statistical significant efficacy and safety profiles.

The studies demonstrated that Curaderm was effective against skin cancer cells while sparing normal cells. Normal cells were observed to replace the dead cancer cells during the process of killing residual cancer cells. These findings align with previous research conducted in cell cultures, animal models, and human studies, which highlighted the important specificity properties of BEC glycoalkaloids in targeting cancer cells without harming healthy cells.

The Phase III studies concluded that an 8-week treatment with Curaderm resulted in an overall efficacy rate of 78% compared to 25% in the placebo vehicle group ($P < 0.001$). The treatment was well-accepted by patients and had a low incidence of local adverse events, with no systemic side effects reported. Impor-

tantly, Curaderm was found to be effective against various types of BCCs, including superficial, nodular, and infiltrative morpheaform variants.

Researchers reported that Curaderm pharmacotherapy outperformed other treatments, including surgery, and in difficult-to-treat locations of skin cancers. Clinical studies focussing on safety, efficacy, compliance, and cosmetic outcomes in different population groups have also been conducted [43]-[49].

These investigations revealed that treatment with Curaderm for 4 weeks resulted in a success rate of approximately 40%, while over 90% of patients with BCCs were successfully treated within 12 weeks. The duration of treatment varied depending on the size and location of the skin cancer. AK required days rather than weeks of Curaderm treatment for successful outcomes. For cutaneous SCCs, the required treatment time ranged from 5 to 16 weeks. The treatment procedure was well-tolerated, with good compliance and robust efficacy, safety, and cosmetic outcomes [50]-[55].

Recurrence rates of Curaderm-treated skin cancers were found to be very low [26] [27].

In addition, amazingly, in cases where skin cancers recurred after treatment with other modalities such as radiation, photodynamic therapy, laser therapy, or cryosurgery, and were subsequently treated with Curaderm resulted in a 52% success rate. This is important because failed treatments with such modalities typically require surgical interventions, which often have poor cosmetic outcomes [50] [54] [56].

The Phase III trials demonstrated the wide-ranging efficacy of Curaderm in treating different histological types and depths of skin cancers, even in sensitive areas of the body. To this end, **Figures 3-6** show examples of Curaderm treated KA, AK, BCC, and SCC. Comparative studies with other existing treatments have established the practical use of Curaderm in dermatology. Follow-up studies conducted over five years on cases treated with Curaderm showed no recurrences.

Figures 3-6 show examples of Curaderm treated KA, AK, BCC, and SCC.

These observations with Curaderm therapy highlight the need for improved approaches in the treatment of skin cancers, specifically in enhancing the bioavailability of anti-cancer agents within cancer cells. While nanoparticle research has shown promise in *ex vivo* studies, its application *in vivo* for treating skin malignancies has been relatively unsuccessful [57] [58].

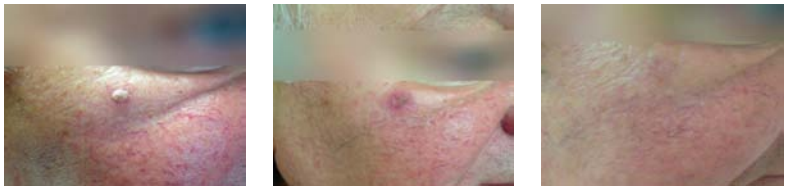

Figure 3. Keratoacanthoma of the face. The treatment was 7 days! The wound healed without the formation of scar tissue.

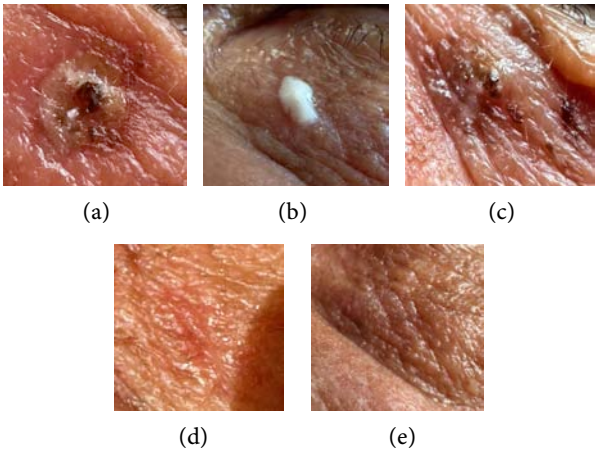

Figure 4. An isolated pigmented AK (5 mm diameter) at zone 2 of the left orbital area before commencement of treatment (a), amount of Curaderm applied to AK (b), after 6 applications (end of treatment, EOT) of Curaderm, (c), 3 days after EOT (d), 14 days after EOT (e).

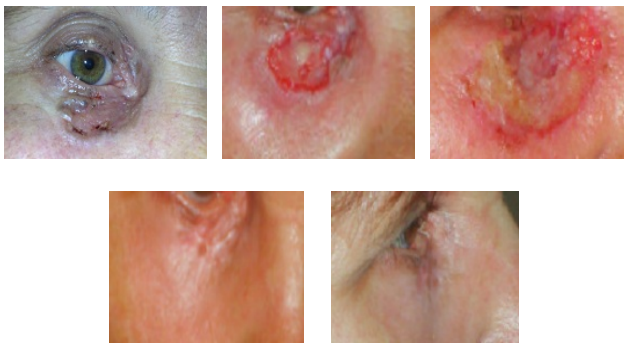

Figure 5. Scleroderma-like form of basalioma of the skin of the corner of the eye with a transition to the upper and lower eyelids. 3 weeks after the start of treatment, the true boundaries of the tumor were revealed. Curaderm treatment was 8 weeks. The tumor completely disappeared with minor tissue scarring.

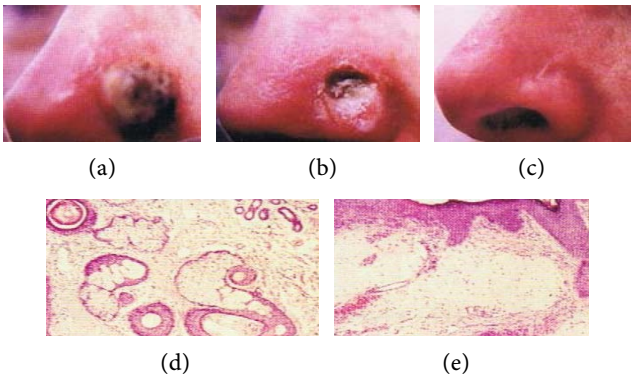

Figure 6. SCC on the nose of a patient before (a), during (b) and after Curaderm treatment (c). Curaderm was applied for 5 weeks. Note the depth of the cancer as cartilage was exposed during treatment. The clinical diagnosis was confirmed histologically by punch biopsy (d). After completion of the therapy histopathology determined that no residual cancer was present (e). Clinical assessment 5 years post treatment revealed that there was no recurrence.

4. Discussion

This communication introduces Curaderm, a treatment for skin cancer that has been developed by understanding the structure, mechanism of action, pharmacokinetics, pharmacodynamics, and toxicology of the medication. Curaderm contains low concentrations of naturally occurring BEC glycoalkaloids, which have demonstrated high bioavailability approaching the efficacy observed in anticancer cell culture studies. The formulation of Curaderm also incorporates desmosomal, stabilizing, and keratolytic agents to optimize the interaction and effectiveness of the low concentration of BEC.

The excipients in Curaderm reversibly denatures the epidermal proteins claudin, desmoglein, filaggrin and proteases and transiently enhance optimal bioavailability of BEC with cancer cells. To fully achieve the optimal conditions, two daily applications of Curaderm to the skin cancers are required followed by application of an occlusive dressing shown in Figure 7.

BEC in Curaderm is highly selective in targeting cancer cells and therefore has no significant side effects. However, the inclusion of desmosomal, stabilizing, and keratolytic agents in the formulation is necessary to achieve maximal effects in destroying all cancer cells. These agents, such as salicylic acid, lactic acid, and urea, have been found to cause transient side effects, including irritation, reddening, itching, pain, and burning sensations at the treatment area. These effects typically last only a few minutes after the application of Curaderm and are primarily attributed to the excipients present in the formulation [26] [27].

The economic burden of skin cancer is substantial, and in the U.S. alone, the annual costs during the period of 2016-2018 for skin cancer was $8.9 billion [59]. Controlling the cost of health care is a global concern. Attempts to avoid accelerating spending with limited outcomes should be encouraged

Curaderm is a topical treatment modality used for AK, a precancerous skin condition. Cost comparisons have indicated Curaderm's positive position in terms of affordability compared to traditional topical treatments for AKs [60]. No direct information of price structure is available for the treatments KA, BCC, and SCC for Curaderm compared with other procedures. Nevertheless, the cost benefits with Curaderm therapy compared with traditional therapies for skin cancer is expected to be even more affordable than was reported for AK.

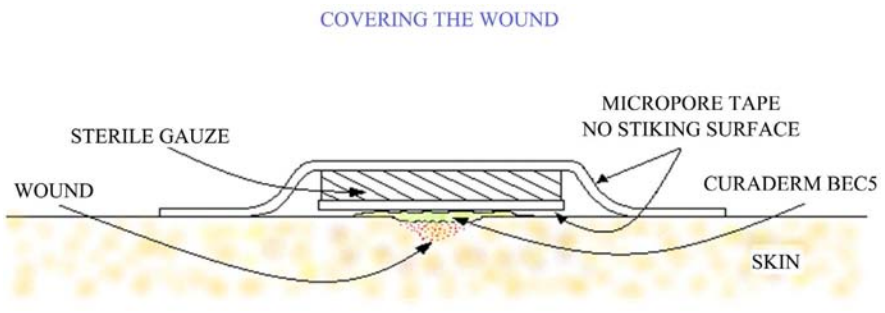

Figure 7. Occlusive dressing used after application of Curaderm to skin cancer lesions.

The historical content of the evolution of surgical removal of skin cancer, leading up to Mohs micrographic surgery, perceived to be the "gold standard" treatment of NMSC, has recently been challenged by Curaderm therapy [61]. Extensive exploration of the biochemical properties and mechanisms of BEC [26] [27] [36] [37] [38] [39] have provided a critical perspective and understanding of Curaderm's true potential and place in current medical practice [61].

5. Conclusions

In conclusion, the studies aimed to create a topical cream formulation, known as Curaderm that could address the needs of patients with skin cancer. The objectives included ensuring the safety and effectiveness of the cream, while also prioritizing factors such as excellent cosmesis, low cost, and user-friendliness.

The development of Curaderm serves as a testament to the significance of comprehending the interactions between active ingredients, excipients (additional substances added to a medication for various purposes), and the biological system. By understanding these dynamics, researchers were able to create a pharmaceutical formulation that is both effective in treating skin cancer and affordable for patients.

Author Contributions

All authors have contributed equally to this article.

Conflicts of Interest

Dr Cham holds patent rights on BEC technology.

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Investigating the Influence of Glaucoma on the Quality of Life among Adult Patients

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Abstract

Background: Research exploring the influence of glaucoma on quality of life has gained momentum in recent years. Numerous studies have investigated the multifaceted aspects of quality of life in glaucoma patients, utilizing various assessment tools and methodologies. **Objective:** To determine the influence that glaucoma has on the quality of life among adult patients. **Study site:** kitwe teaching eye hospital, Zambia. **Method**: It was a cross-sectional study that was conducted from 30th June 2022 to 17th April 2023. The study included 106 diagnosed glaucoma patients who were above the age of 55 years. Data was collected using validated 25-item national eye institute visual function Questionnaire (NEI VFQ-25). The data was analyzed using SPSS version 26 and Microsoft excel to present frequencies and percentages that generated graphical presentation. **Results**: 62% of the participants worry about their eye sight most of the time, 26% sometimes and 12% a little time. 9% of the participants had little difficulty to read ordinary prints, 14% moderate difficulties and 58% extremely difficult. 40% of the participants could drive despite glaucoma damaging their eyes while 60% could not. Majority of the patients said it was difficult noticing things around them while walking or sitted in one place. There was a significant difference between effects of glaucoma on patients and the existing relationship between glaucoma and quality of life (ANOVA, p = 0.019 and ANOVA, p = 0.023). **Conclusion:** This study has demonstrated the magnitude of impact that glaucoma has on the Quality of Life (QoL) in diagnosed patients and the relationship between glaucoma and the Quality of Life. Due to the progressive visual loss, the amount of activities these patients would perform is negatively affected especially where social and economic activities are concerned which also affects their monthly earnings for those living in middle to low-income countries. Therefore, social welfare and psycho-social institutions need to increase their support for these glaucoma patients.

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Keywords

Glaucoma, Quality of Life, Glaucoma Patients

1. Introduction

Glaucoma is a chronic eye disease that affects the optic nerve, leading to progressive vision loss, and if left untreated, can eventually result in blindness [1] [2] [3]. It is one of the leading causes of irreversible visual impairment worldwide affecting millions of individuals across different age groups [4] [5] [6]. As the global population continues to age, the prevalence of glaucoma is expected to rise, posing significant challenges for healthcare systems [7] [8] [9] [10].

A study was conducted on the effects of glaucoma medication on dry eye syndrome and quality of life in patients with glaucoma, they found that there were significant differences in near work daily activities and social functioning between the control normal participants group and glaucoma patients group who were on medication [11]. However, this study only focused on the near work activity aspect of the quality of life and overlooked other aspects which are as well very much affected in the individuals suffering from this disease. Also the study did not specify the age group of the participants and it focused more on the drug therapeutics side effects on participants than the social economic factors.

Another study was done in Ethiopia on vision-related quality of life and associated factors among an adult Population with glaucoma attending a comprehensive specialized hospital concluded that the vision-related quality of life was significantly associated with educational status, visual acuity of the better and worse eye as well as stage of glaucoma in the better eye [12]. However, the gap in this study was that it only looked at the quality of life in glaucoma patients with regard to their educational status, visual acuity and glaucoma stage but disregarded other aspects like financial status of the affected patients.

While the primary clinical focus of glaucoma research has traditionally been on the progression of the disease and its management, there is growing recognition of the impact of glaucoma on the quality of life (QoL) of affected individuals [13] [14] [15]. Quality of life encompasses various aspects, including physical, psychological, social, and emotional well-being [16]. Understanding how glaucoma influences the QoL of patients is crucial for optimizing their care, addressing their specific needs, and improving their overall treatment outcomes.

Patients have to use one or more eye drops more than once a day which brings about issues to do with adherence [17] [18]. Therapies such as effective laser trabeculoplasty and glaucoma surgery may eliminate or reduce the need for glaucoma medications thereby curbing the problem of daily medication compliance [19]. However, this treatment modality is not cheap and many patients cannot afford to pay for it thereby posing a major threat on the patient's QoL as most patients diagnosed with glaucoma are above the age 55 years and near to or

already retired by then with limited income to sustain their daily needs [20] [21] [22]. Therefore, this study conducted at kitwe teaching eye hospital in Zambia focused on finding out the influence that glaucoma has on the quality of life of adult patients above the age of 55 years.

2. Materials and Methods

This was a cross-sectional study which included 106 participants and focusing on the subject matter of glaucoma, particularly on how it influences the patients' quality of life in patients above the age of 55 years. Informed consent was obtained from all the participants before they could be recruited in the study in accordance with Helsinki declaration. The data involved glaucoma patients who visited the hospital from 30th June, 2022 to 17th April, 2023. This study employed a structured questionnaire to collect primary data from the respondents. Vision-Related Quality of Life was assessed using the validated 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) developed by researchers at the National Eye Institute (NEI), which is part of the National Institutes of Health (NIH) in the United States and the validity and reliability of the questionnaire was tested in conducting this research. The variables which were investigated in this study included the type of community patient was coming from, gender, number of years lived with glaucoma, who they lived with, monthly income, extent of worry about eye sight, difficulties in visiting with people, whether driving or not, if driving any difficulties with sight, any difficult to read ordinary prints, any difficulties finding things on shelves, noticing objects on the sides and road signs as well as any difficulties in picking matching colours for special dress codes.

Inclusion and Exclusion criteria

The following criteria was used to determine inclusion: 1) Patients above the age of 55 years, 2) patients with a definitive diagnosis of glaucoma, 3) patients with best corrected visual acuity of 6/18 and worse who visited the hospital from 30th June, 2022 to 17th April, 2023.

The following were the exclusion criteria: 1) known glaucoma patients but have other ocular conditions that may affect best corrected visual acuity, 2) Patients with insufficient medical data, 3) patients below the age of 55 years, 4) Patients with a history of glaucoma surgery.

Purposive sampling technique was used in selecting respondents for the questionnaires. The rationale for employing this type of sampling technique was based on the idea that the selected respondents meet the inclusion criteria characteristics.

To find the minimum sample size for this study, Slovin's Formula was used whose formula is shown below:

$$n = N \Big/ \left(1 + Ne^2\right)$$

where

n = sample size;

N = Population size;

e = margin of error = 0.05.

The population of 144 patients were monthly cases seen at Kitwe Teaching Eye Hospital. Therefore, the sample size will be;

144/(1 + 144 * 0.0025) = 105.8823529 = (106)

Visual acuity and visual field was used to characterize the patients to be included in the study. The data was analyzed using SPSS version 26 and Microsoft excel to present frequencies and percentages that generated graphical presentation.

3. Results

A total of 106 patients were included in this study, all those patients that did not meet the inclusion criteria were left out. These included glaucoma diagnosed patients were asked to provide responses in various ways in which glaucoma affected their quality of life with regard to their socio-economic status. 33% of the participants were coming from the rural areas while 67% of them were from the urban communities, of which 57% were male and 43% were female. 34% of the participants had glaucoma for less than 5 years while 66% of them had lived with it for more than five years. 60% of the participants survive on less than $200 USD per month, 23% between $200 - $400 USD and finally 17% above $400 USD per month (Table 1). 36 out of 106 participants suffered from Chronic angle closure glaucoma, 20 from Pseudoexfoliation glaucoma and finally 70 suffered from Primary open angle glaucoma (Figure 1). The study found that 16 out of 106 participants had visual acuity of less than <20/200, 30 had between 20/125 to 20/200, 40 had between 20/80 to 20/125 and 20 had 20/50 to 20/80 (Figure 2). 62% of the participants were worried about the eye sight and majority of them could not drive their cars in both day and night time due to progressively depleting vision (Table 2). The study further revealed that 9% of the participants had little difficulty to read, 14% had moderate difficulties and 58% found it extremely difficult to read ordinary print. However, 2% of them had never faced difficulties in reading while on the other hand 16% had stopped reading because of their eyesight. The table further shows that 10% of the participants found it a little difficulty to find something on a crowded shelf, 11% found it moderately difficulty, 72% had extreme difficulties, 7% faced no difficulty at all to find something on a shelf. In the same table results, 12% of the participants showed that it was a little difficulty to notice the objects off their side while walking, 67% revealed that it was extremely difficulty and 21% demonstrated that it was moderately difficulty to notice objects while walking. In the same vain, 11% demonstrated that it was a little difficulty to differentiate colors, 8% showed that it was moderately difficult while the majority which is 51% revealed that it was extremely difficulty to differentiate colors and 30% found no difficulty at all (Table 3).

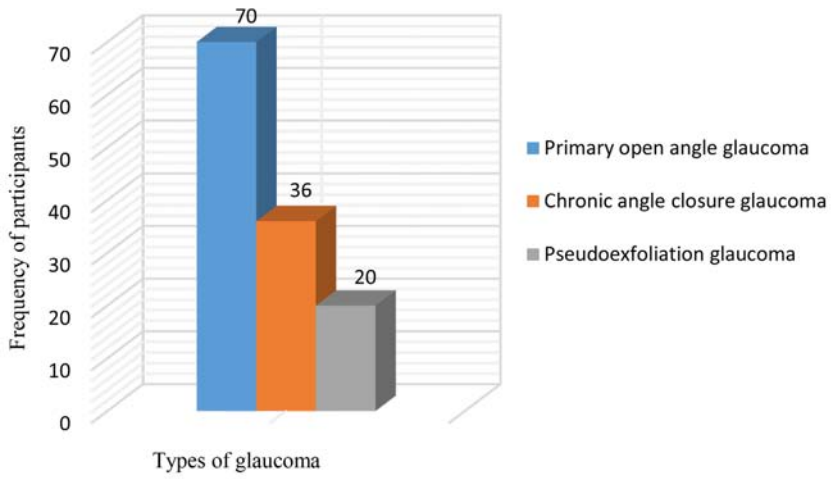

Figure 1. Types of glaucoma and participant frequency.

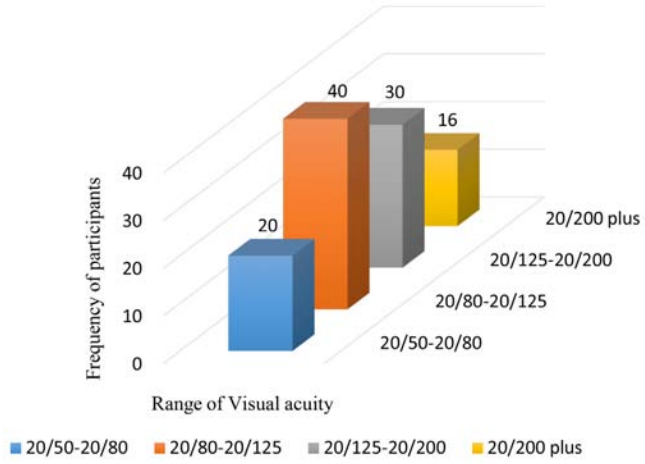

Figure 2. Visual Acuity of better eye and participant frequency.

Table 1. Shows social demographic characteristics of glaucoma patients.

Variable	Category	Frequency (n)	Percentage (%)
Type of community	Rural	35	33
	Urban	71	67
Gender	Male	60	57
	Female	46	43
Number of Years lived with Glaucoma	Less than 5 years	36	34
	More than 5 years	70	60
Who do you live with	Alone	21	20
	Spouse	45	42
	With family Members	40	38
Monthly Income	Less than $200 USD	64	60
	Between $200 to $400 USD	24	23
	More than $400 USD	18	17

Table 2. Existing relationship between glaucoma and quality of life.

Variable	Case (n = 106)	Percentage (%)
Worrying about eyesight.		
A little of the time:	13	12
Most of the time:	66	62
Some of the time:	27	26
Difficulties in visiting with people.		
Extreme difficulty:	58	55
Moderate difficulty:	14	13
No difficulty at all:	16	15
Stopped because of eyesight:	18	17
Currently driving.		
Yes:	42	40
No:	64	60
If currently driving, any difficulties driving during daytime.		
Extreme difficulty:	41	38
Moderate difficulty:	44	41
No difficulty at all:	21	21
Difficulty when driving at night.		
Extremely difficulty:	42	40
Moderate difficulty:	34	36
No difficulty at all:	30	24
Difficulty driving in bad conditions (bad weather, during rush hour, on the freeway, or in city traffic).		
Extremely difficulty:	42	40
Moderate difficulty:	36	38
No difficulty at all:	28	22

Table 3. Shows negative effects of glaucoma on patients daily activities.

Variable	Case (n = 106)	Percentage (%)
How much difficulty do you have reading ordinary print in newspapers?		
A little difficulty:	10	9
Extremely difficulty:	62	58
Moderately difficulty:	15	14
No difficulty at all:	2	2
Stopped because of eyesight:	17	16

Continued

Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?		
A little difficulty:	11	10
Extremely difficulty:	76	72
Moderately difficulty:	12	11
No difficulty at all:	7	7
Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?		
A little difficulty:	13	12
Extremely difficulty:	71	67
Moderately difficulty:	22	21
Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?		
A little difficulty:	12	11
Extremely difficulty:	54	51
Moderately difficulty:	8	8
No difficulty at all:	21	20
Stopped because of eyesight:	11	10

4. Discussion

The World Health Organization (WHO) defines Quality of Life (QOL) as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [23]. A person's Vision Related Quality of Life (VRQOL) is specifically concerned with his or her satisfaction with their vision function and how it impacts their daily lives [24]. we carried out this study to investigate the influence of glaucoma on the quality of life among adult patients, making it one of the few studies conducted around the globe looking specifically on this negative aspect of glaucoma.

Glaucoma is the leading cause of irreversible blindness worldwide. It is associated with a pathologically high intraocular pressure which negatively affects visual acuity and cause visual field defects [25]. The quality of life of patients with glaucoma is often affected by the impairment of visual function. According to the findings of this study, glaucoma patients had a significantly lower quality of life. Moreover, the majority were psychologically affected in terms of worry and because of that, the level of work input was largely affected as a consequence of poor vision which negatively affected their quality of Life. Thus, a segment of the population sampled had even stopped working [26]. Visual impairments are much more detrimental to reading skills and information access, slightly less detrimental to mobility and independence, and least detrimental to emotional well-being [27]. And the study agrees with our findings because a lot of partici-

pants (58%) had extreme difficulties reading ordinary prints despite being educated. Glaucoma patients are more likely to experience anxiety, depression and feelings of hopelessness about their future, and their self-reported health assessment is reduced [28]. This could be attributed to a number of factors because according to this study, most glaucoma patients are uncertain about the source of income to buy their medication as most of them (60%) earned less than $200 per month and this makes them (66%) be worried most of the their life time thereby sending themselves into depression. There is a strong association between glaucoma and Vision related QoL [29] thus confirming that glaucoma patients have reduced vision related quality of life.

The study confirms having correlated to other studies that glaucoma causes a reduced Quality of Life (QoL) in terms of the patients' social life, their occupational lives and general quality of living. A good number of participants that owned cars did not find it easy to drive and see road signs and objects during day and night time respectively. Some participants in the study (76%) stated that they could not easily find things on the shelves in their houses and could not even pick matching clothes for their outfit with easy (54%). Thus all levels of visual impairment had a negative impact on the quality of life of glaucoma patients and have deteriorating as well as detrimental effects as observed. The functional vision determines the ability of an individual to perform vision dependent activities [30]. The degree of concentration depends on a number of factors including visual acuity, contrast sensitivity, and field of vision. By limiting an individual's functional vision and negatively affecting their sense of wellness, visual disability in glaucoma negatively affects the quality of life (QoL).

Glaucoma is among the most common causes of blindness in sub-Saharan Africa, accounting for 5.2% of total blindness and adversely affecting patients' quality of life. As a result, patients with glaucoma become functionally impaired when central vision is impinged upon or affected by visual field loss [31].

As observed in the findings, patients with glaucoma may have difficulty recognizing faces, navigating, reading, viewing television, and adjusting to different levels of lighting as a result of their disease.

Most of the sampled patients with glaucoma 94.34% become limited in the kind of work or activities they would like to do because of moderate to severe visual impairment with primary open angle glaucoma being the most frequent type among adults diagnosed with glaucoma. Studies have shown that there is a positive correlation between quality of life and glaucoma patients.

5. Conclusion

This study has demonstrated the magnitude of impact that glaucoma has on the Quality of Life (QoL) in diagnosed patients and the relationship between glaucoma and the Quality of Life. Glaucoma negatively affects many facets of the patient's life once diagnosed with it. Due to the progressive visual loss, the amount of activities these patients would perform is negatively affected especially where social and economic activities are concerned which also affects their monthly

earnings for those living in middle to low-income countries. Therefore, social welfare and psycho-social institutions need to increase their support for these glaucoma patients.

6. Study Limitations

The limitation to this study was that the sample size was small and only collected from one single hospital in addition to the duration of study being short. There is a need for a bigger sample size from more than one hospital with a prolonged duration of study in future research for the most reliable and unbiased findings.

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Patient Consent and Ethics Approval

Consent was obtained from all the patients before being recruited into the study and ethical approval done by Mulungushi university ethics committee.

Disclosure Statement

The authors have no financial or proprietary interest in any material or method mentioned.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authorship

Authors attest that they meet the current ICMJE criteria for authorship.

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Appendix: Questionnaire

Dear Respondent:

You have been picked randomly via the use of probability sampling techniques to participate in this research project and your full participation will be highly appreciated. The findings generated in this study will be handled with the highest level of confidentiality and for this academic exercise only.

Please respond to the following questions as truthfully as possible. Where there are, options provided, select the appropriate response by putting a tick [√] in the box of your choice, and write the answer in the space proved

Part 1: Demographic characteristics of participants Provide information about yourself by ticking (√)

1) What type of community do you live in?

a) Rural

b) Urban

2) Gender

a) Female

b) Male

3) Age

a) Above 55 years

b) Less than 55 years

4) Number of years lived with glaucoma

a) Less than 5 years

b) More than 5 years

5) Who do you live with?

a) Alone

b) Spouse

c) With family Members

6) Monthly Income

a) Less than $200 USD

b) Between $200 to $400 USD

c) More than $400 USD

7) Worrying about eyesight.

a) A little of the time:

b) Most of the time:

c) Some of the time:

8) Difficulties in visiting with people.

a) Extreme difficulty:

b) Moderate difficulty:

c) No difficulty at all:

d) Stopped because of eyesight

9) Currently driving.

a) Yes:

b) No:

10) If currently driving, any difficulties driving during daytime.

a) Extreme difficulty:

b) Moderate difficulty:

c) No difficulty at all:

11) Difficulty when driving at night.

a) Extremely difficulty:

b) Moderate difficulty:

c) No difficulty at all:

12) Difficulty driving in bad conditions (bad weather, during rush hour, on the freeway, or in city traffic).

a) Extremely difficulty:

b) Moderate difficulty:

c) No difficulty at all:

13) How much difficulty do you have reading ordinary print in newspapers?

a) A little difficulty:

b) Extremely difficulty:

c) Moderately difficulty:

d) No difficulty at all

e) Stopped because of eyesight:

14) Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

a) A little difficulty:

b) Extremely difficulty:

c) Moderately difficulty:

d) No difficulty at all:

15) Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

a) A little difficulty:

b) Extremely difficulty:

c) Moderately difficulty

16) Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

a) A little difficulty:

b) Extremely difficulty:

c) Moderately difficulty:

d) No difficulty at all

e) Stopped because of eyesight:

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The Burden of Undiagnosed Hypertension and Associated Risk Factors among Adults in a Rural Community in Imo Sate, South-East Nigeria

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Abstract

Background: Cardiovascular diseases are the leading cause of death globally and hypertension is a major contributor to this burden. Many people with hypertension have poorly controlled blood pressure and up to half of the adults with hypertension are unaware of their hypertensive status due to factors that bother on poor management and poor screening approaches. The implication is that people who have poor access to healthcare especially those in the rural communities are at increased risk of cardiovascular complications and all-cause mortality. Unfortunately, not much has been done to ascertain the burden of undiagnosed hypertension and associated risk factors in rural communities in Nigeria. **Methods:** We conducted a community-based cross-sectional study in a rural community in Imo State, Nigeria, on burden of undiagnosed hypertension with participants recruited via a multi-stage sampling method. An interviewer-administered questionnaire was used, and standardized instruments were applied to obtain, process and analyze the data. Tests of association between the independent variables and outcome were conducted using logistic regression. *P*-value of < 0.05 was used as the criterion for statistical significance. **Results:** A total of 380 adults participated in the study. The mean age was 44.2 years. The prevalence of undiagnosed hypertension was 35.8%. Logistic regression revealed that age, with the respondents in the age groups 26 - 35 years (OR = 10.647, 1.910 - 59.345, p-value = 0.007), 36 - 45 (OR = 3.680, 1.263 - 10.723, p-value = 0.017), 46 - 55 years (OR = 2.737, 1.114 - 6.727, p-value = 0.039), 56 - 65 years old (OR = 3.384, 1.610 - 7.115, p-value = 0.001); and being married (OR = 3.846, 1.118 - 13.233, p-value = 0.033), were independent risk factors for undiagnosed

hypertension. **Conclusion:** The prevalence of undiagnosed hypertension in the rural population of South-East Nigeria is high. Younger age (26 - 35 years) had the highest odds of risk for occurrence of hypertension. Also being married was identified as a risk factor for undiagnosed hypertension.

Keywords

Hypertension, Undiagnosed Hypertension, Risk Factors, Rural Community

1. Introduction

Cardiovascular co-morbidities are the leading cause of mortality worldwide [1]. Hypertension, is the single most significant contributing factor, causing over 9.4 million deaths globally and accounting for more than 50% of stroke and cardiac disease cases respectively [2] [3]. Despite these health risks, many people the world over have undiagnosed hypertension. Hypertension is a global problem with the prevalence projected to be on the rise due to several factors including lifestyle and environmental changes, about 1.5 billion people are expected to be hypertensive by 2025 worldwide [1] [2]. It is estimated that 1 out of every 3 adult Americans is hypertensive [3] [4] and similar ratios have been reported in different parts of Europe and Asia including UK [5], Indonesia [6], India [7], Malaysia [8], and Poland [9]. In Africa studies from different countries such as Ethiopia, and Ghana have also reported high prevalence rates [10] [11] [12]. Similarly, many reviews from Nigeria indicate that 1 out of every 5 Nigerian is hypertensive [13] [14] [15] [16]. The implication is that more people will die because of complications from hypertension, which is largely a preventable scenario.

Hypertension is defined as systolic blood pressure of 140 mmHg and above and/or diastolic blood pressure of 90 mmHg or above [12] while undiagnosed hypertension is defined as the presence of hypertension in a person who has not been previously diagnosed as hypertensive. In addition to the high prevalence of hypertension globally, many studies have reported a high prevalence of undiagnosed hypertension in various settings and populations. On average, about half the adult population who are hypertensive may not be aware of their hypertensive status at the first time they were told, this is corroborated by studies from Peru [17] and Bangladesh [18] which reported prevalence rates of 67.2% and 56.9% respectively. Another study from Lebanon by Kanji *et al.* [19] reported the prevalence of undiagnosed hypertension as 42.69%. Some other studies from India by Bharati *et al.* [20] and Schuda *et al.* [21] reported significant proportions of undiagnosed hypertension as 27.6% and 26% respectively. In Africa, one systematic review by Ataklte *et al.* [22] in 2015 yielded a pooled prevalence of 15% to 70% for undiagnosed hypertension. Other researchers in Africa such as Dejenie *et al.* [23], Getachew *et al.* [24], and Bushara *et al.* [25] reported prevalence rates between 13% and 38.2%. Studies from different parts of Nigeria reported

the prevalence of undiagnosed hypertension as between 20% and 60% depending on the study population and the setting [26]-[31]. A significant number of these studies were conducted in rural areas with prevalence levels in these communities approximating the lower limits reported in the literature.

Some predictors have been identified as significant risk factors for hypertension. These factors include age, gender, educational status, place of residence, family history of hypertension, smoking, alcohol use disorder, substance use, abnormal lipid profile, obesity, high sodium consumption and sedentary lifestyle [1] [2] [15]-[25]. In Nigeria, rural communities have documented reports of low prevalence rates for hypertension but emerging reports indicate a worrisome trend that undiagnosed hypertension may be on the rise in these communities [32]-[37] with poor access to healthcare, poverty, ignorance, and poor health-seeking behaviour implicated as contributory factors. Additionally, hypertension with complications such as stroke and myocardial infarction remains shrouded in myths and misconceptions in many rural settings [38] [39] [40]. A complex web is the scenario where many rural settlements are caught in a demographic transition occasioned by urbanization and globalization resulting in behavioural changes, such as fewer farming activities, less recreational activities, less exercise, more sedentary lifestyle, and more refined saturated diets; yet with poor access to healthcare, poverty, ignorance, and poor health-seeking behaviour subsisting [38] [39] [40].

Despite a plenitude of literature on hypertension globally [1]-[6] there appears to be a paucity of information on the burden and correlates of undiagnosed hypertension in rural communities of southeastern Nigeria. This is of great concern considering that from observations a significant proportion of adult patients seen at the General Outpatient Clinics of the Federal University Teaching Hospital, Owerri, the foremost tertiary health facility in urban Imo State, on referral, present with at least one of these cardiovascular complications—hypertensive heart disease, heart failure, stroke or ischaemic heart disease, and many of the patients are resident in the rural communities. The majority of them had no prior knowledge of being in a state of persistently elevated blood pressure. Against this background, this study set out to assess the burden of undiagnosed hypertension and its associated risk factors in a rural community with the view to identifying risk factors that may be amenable to early intervention and population-based prevention strategies to minimize cardiovascular morbidity and mortality.

2. Methodology

2.1. Study Area

The research was carried out in Mbieri community of Mbaitoli Local Government Area (LGA) of Imo state. Mbieri is a rural community with a projected population of 43,130 adults (20,487 males and 22,643 females) as at 2017 based on 2006 Nigerian census [41].

2.2. Study Population

Adults aged 18 years and above resident in Mbieri community.

2.3. Study Duration

Collection of data for the study lasted from January 2022 to April 2022.

2.4. Study Design and Variables

This was a community-based cross-sectional analytical study. The dependent variable was undiagnosed hypertension while the independent variables were family history of hypertension, physical activity, diabetes mellitus, obesity, alcohol use and dyslipidaemia. Undiagnosed hypertension is defined as blood pressure (BP) of greater than or equal to 140/90 mm/Hg on at least two different occasions with the individual unaware of his/her blood pressure status. The nature of measurements for the independent variables are described under data collection below.

2.5. Sample Size

The sample size was calculated using the formula:

$$n_0 = Z^2 Pq/d^2 \text{ (with the population size greater than 10,000)}$$

where,

n_0 = the desired sample size (when population is greater than 10,000).

Z = the standard normal deviate usually set at 1.96 which corresponds to 95% confidence interval, it contains the area under the normal curve.

p = the estimated proportion of an attribute present in the population. The prevalence of hypertension used was 44.5%. This was the prevalence value obtained from a community-based study done in Enugu state by Ahaneku *et al*. [42].

d = desired level of precision, this was set at 0.05.

$q = 1 - P$.

Therefore n = $(1.96)^2 \times 0.445 \times (1 - 0.445)/(0.05)^2$

= 0.94877916/0.0025

= 379.5 approximately 380

The minimum sample size was 380 respondents.

2.6. Sampling Method

Multi-stage sampling technique was used to recruit the respondents. This study was carried out in Mbieri community of Mbaitoli Local Government Area of Imo State. In Mbieri community, there are 17 villages. Proportionate sample was recruited from each of the villages into the study as calculated accordingly using

Proportionate samples recruited from each village = [total population of the village/Total population of the community] × [380].

Subsequently, data was consecutively collected from each of the villages starting from the first in the list drawn up for the villages using the multistage sam-

pling. In the first stage, compounds were sampled. This was followed by households in the second stage. The third stage involved sampling of one individual out of every eligible adult in the household. On arrival at each village, a starting point was chosen from the centre of the village which was the "village square". At the "village square", the first compound to be sampled was chosen by spinning a bottle and it was allowed to make at least three rotations before it stopped. The compound in the direction the tip of the bottle points was sampled first. Subsequently, alternate compounds were selected and sampled. In each compound, a list of all the households in that compound was made and alternate households were sampled. One individual out of every eligible adult in the household was recruited into the study using the simple random sampling. Where there was only one household in the compound that household was sampled. The same process was repeated for each selected compound in the village until the estimated number of respondents to be recruited from the village was reached, thereafter, the researcher moved to another village. Structured interviewer administered questionnaire and validated instruments were used to collect demographic and clinical information.

2.7. Inclusion Criteria

Consenting adults' resident in Mbieri community.

2.8. Exclusion Criteria

Individuals previously diagnosed as having hypertension, respondents on anti-hypertensive agents, those who are unable to provide verbal or written consent pregnant women due to possible presence of pregnancy induced hypertension, and individuals too ill to cope with the physical and mental exertion of data collection.

2.9. Data Collection

Data were consecutively collected from each of the villages starting from the first using multistage sampling. In the first stage, compounds were sampled. This was followed by households in the second stage. The third stage involved sampling one individual out of every eligible adult in the household. A pretested interviewer-administered questionnaire, designed by the researcher, and validated instruments were used to collect demographic and clinical information after consent was obtained. The blood pressure was measured using standard procedure. The Alcohol Use Disorders Identification Test (AUDIT) questionnaire [43] was used to assess alcohol use, and International Physical Activity Questionnaire-Short Form (IPAQ-SF) [44] was used for physical activity measurement. The response for AUDIT was categorized as harmful use or not, while physical activity was categorized as category 1-sedentary, category 2-moderate activity, category 3-health enhancing physical activity (HEPA) [45] [46]. Standard aseptic processes were used to collect the blood samples which were sent to the laboratory for analysis of glucose and lipid profile using standard techniques.

Non-fasting lipid levels were used for this study and have been suggested not to be significantly different from fasting lipid levels [47] [48] [49]. Height and weight were also measured using standard validated instruments, and body mass index (BMI) was estimated. Four categories of BMI (<18.5 kg/m^2, 18.5 - 24.9 kg/m^2, 25.0 - 29.9 kg/m^2 and >30.0 kg/m^2) were identified as underweight, normal weight, overweight and obesity respectively. Several studies used this classification method [50]-[55].

2.10. Statistical Analysis

Data were analysed using SPSS version 22. Statistical significance was taken as a *p*-value less than 0.05. The results were represented in frequency tables. Mean and standard deviation were calculated for continuous variables and *Chi-square* was done for categorical proportions. Logistic regression was conducted for variables with significant association to detect independent risk factors for undiagnosed hypertension.

2.11. Ethical Clearance

This was obtained from the Institutional Ethics Committee of the Federal University Teaching Hospital, Owerri (FUTHO), formerly Federal Medical Centre, Owerri.

3. Results

All 380 participants sampled consented and were recruited into the study giving a 100% response rate. The prevalence of undiagnosed hypertension was 35.8% (n = 136).

3.1. Socio-Demographic Distribution of Participants

Majority of the respondents in the study were between the 56 - 65 age group (27.6%, n = 105) and there were more female responders 57.6%, (n = 219) than males. Most were married 51.3%, (n = 195) and predominantly Christians 92.1%, (n = 350). Nearly all of them had at least primary level education with just three of them (0.8%) not having any formal education. Many had family history of hypertension, 42.1%, (n = 160) while 6.3% (n = 24) of the participants were not aware of the presence of hypertension in the family. The most-reported cardiovascular event in the family was stroke, 42.7%; followed by heart failure, 36.6%. In terms of occupation, the responders were predominantly farmers, civil servants in active service or retired, professionals, farmers, and students (**Table 1**).

3.2. Pattern of Blood Pressure Distribution of Participants

The pattern of undiagnosed hypertension among the respondents is represented in the bar chart below (**Figure 1**). About 35.8% of the respondents have undiagnosed hypertension with 15.5% (n = 59) in stage 2; and 20.3% (n = 77) in stage 1.

Table 1. Frequency distribution of respondents according to socio-demographic characteristics.

Socio-demographic characteristics	Frequency (n = 380)	Percentage (%)
Age group		
<26	64	16.9
26 - 35	48	12.6
36 - 45	75	19.7
46 - 55	88	23.2
56 - 65	105	27.6
Gender		
male	161	42.4
female	219	57.6
Level of education		
No formal	3	0.8
primary	110	28.9
secondary	136	35.8
tertiary	131	34.5
Occupation		
Farming	72	18.9
trading	42	11.1
professional	55	14.5
C/S	69	18.2
retired	62	16.3
student/apprentice	59	15.5
Unemployed/others	21	5.5
Marital status		
single	107	28.2
married	195	51.3
widowed	78	20.5
Religion		
Christianity	350	92.1
Islam	3	0.8
Traditional	27	7.1
Family history		
positive	160	42.1
negative	196	51.6
not aware	24	6.3
Complications of hypertension suffered by relative (s)		
heart failure	30	36.6
stroke	35	42.7
kidney failure	14	17.1
Others (eye disorders, death)	3	3.6

A significant number of the respondents had prehypertension 30.5% (n = 116) while about a third (33.7%) were normo-tensive (n = 128).

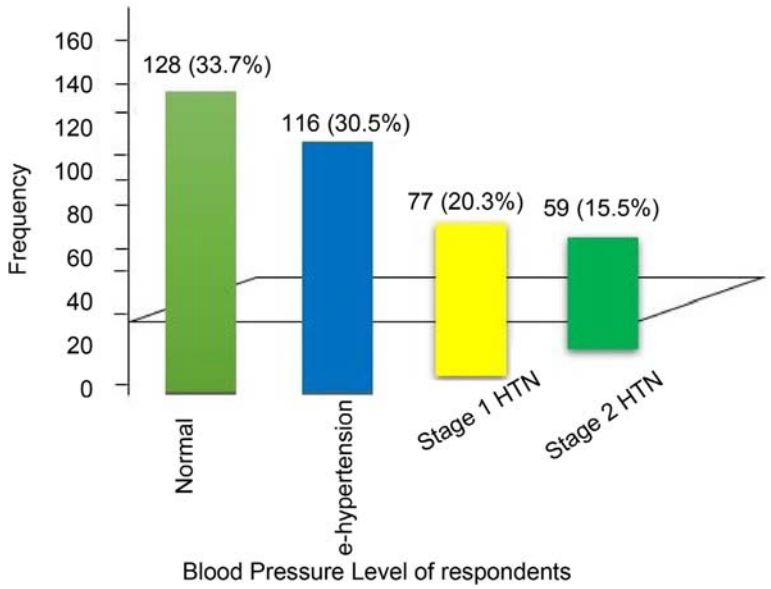

Figure 1. Pattern of blood pressure measurement among respondents.

3.3. Association between Socio-Demographic Characteristics and Undiagnosed Hypertension

The association between socio-demographic characteristics and undiagnosed hypertension is shown in Table 2. Factors such as age ($p \leq 0.001$), occupation ($p \leq 0.001$), level of education ($p = 0.001$), family history (FH) of hypertension ($p = 0.001$), marital status, ($p \leq 0.001$) and religion ($p \leq 0.001$) were found to be significantly associated with the presence of hypertension.

3.4. Association between Lifestyle Indices and Undiagnosed Hypertension

Table 3 below shows the association between lifestyle indices and undiagnosed hypertension. A good number of the participants had central obesity (n = 133), out of whom 59 (43.38%) were hypertensive. Central obesity was found to be significantly associated with undiagnosed hypertension ($p = 0.011$). Also, regarding general obesity, the majority of the participants were either obese (n = 86) or overweight (n = 124), and general obesity was significantly associated with undiagnosed hypertension ($p = 0.001$). The majority of the respondents (n = 343) were not involved in harmful alcohol use and alcohol use was not found to be significantly associated with undiagnosed hypertension ($p = 0.086$). Among the respondents, only a few were involved in high physical activity (n = 26), while the majority were involved on low physical activity. The level of physical activity was significantly associated with undiagnosed hypertension ($p \leq 0.001$).

3.5. Association between Lipid Profile and Diabetes Mellitus, and Undiagnosed Hypertension

The majority of the respondents had dyslipidaemia (n = 195), and this was

Table 2. Association between socio-demographic characteristics and undiagnosed hypertension.

Socio-demographic characteristics	Hypertension status Hypertensive 136 (100%)	Not hypertensive 244 (100%)	Total 380	Chi-square	p-value
Age group (years)					
<26	6 (4.4)	58 (23.8)	64	52.166	<0.001*
26 - 35	12 (8.8)	36 (14.8)	48		
36 - 45	22 (16.2)	53 (21.7)	75		
46 - 55	32 (23.5)	56 (22.9)	88		
56 - 65	64 (47.1)	41 (16.8)	105		
Gender					
male	58 (42.6)	103 (42.2)	161	0.007	0.935
female	78 (57.4)	141 (57.8)	219		
Level of education					
No formal	1 (0.7)	2 (0.8)	3	18.058	<0.001*
primary	55 (40.5)	55 (22.5)	110		
secondary	49 (36.0)	87 (35.7)	136		
tertiary	31 (22.8)	100 (41.0)	131		
Occupation					
Farming	28 (20.6)	44 (18.0)	72	26.451	<0.001*
trading	23 (16.9)	19 (7.8)	42		
professional	16 (11.8)	39 (16.0)	55		
C/S	21 (15.4)	48 (19.7)	69		
retired	32 (23.5)	30 (12.3)	62		
student/apprentice	9 (6.6)	50 (20.5)	59		
Unemployed	7 (5.2)	14 (5.7)	21		
Marital status					
single	12 (8.8)	95 (38.9)	107	47.868	<0.001*
married	78 (57.4)	117 (48.0)	195		
widowed	46 (33.8)	32 (13.1)	78		
Religion					
Christianity	122 (89.7)	228 (93.5)	350	4.836	<0.001*
Islam	0	3 (1.2)	3		
Traditional	14 (10.3)	13 (5.3)	27		
FH of Hypertension					
positive	75 (55.2)	85 (34.8)	160	14.803	0.001*
negative	54 (39.7)	142 (58.2)	196		
not aware	7 (5.1)	17 (7.0)	24		

found to be statistically significant (p-value < 0.001). The presence of abnormal levels of low-density lipoprotein ($p \leq 0.01$), high density lipoprotein ($p \leq 0.001$), and total cholesterol ($p \leq 0.01$) were found to be significantly associated with hypertension. Similarly, the presence of diabetes mellitus was found to be

Table 3. Association between life style index and hypertension.

Life style	Hypertension status Hypertensive	Not hypertensive	Total	Chi-square	p-value
Central obesity (WC)					
Yes	59 (43.38)	74 (30.33)	133	6.542	0.011*
No	77 (56.62)	170 (69.67)	247		
General obesity (BMI)					
Underweight	3 (2.2)	13 (5.3)	16		
Normal weight	40 (29.4)	114 (46.7)	154	18.248	<0.001*
Overweight	61 (44.9)	63 (26.0)	124		
Obesity	32 (23.5)	54 (22.0)	86		
Alcohol use					
Harmful use	18 (13.2)	19 (7.8)	37	2.950	0.086
Un harmful use	118 (86.8)	225 (92.2)	343		
Physical activity status					
Low	99 (72.79)	117 (48.0)	216	22.10	<0.001*
Moderate	33 (24.27)	110 (45.0)	143		
High	4 (2.94)	17 (7.0)	21		

*= Statistically significant, X^2 = Chi-square.

significantly associated with hypertension (p = 0.007). These are as shown in Table 4 below.

3.6. Risk Factors for Undiagnosed Hypertension

Logistic regression was conducted for factors with significant association with undiagnosed hypertension and the results are shown Table 5(a) and Table 5(b). Age (p ≤ 0.001), and marital status (being married, p ≤ 0.001), were identified as risk factors for undiagnosed hypertension. As regards age the respondents in the age group 26 - 35 years were about 10 times more likely to have undiagnosed hypertension (OR = 10.647, 1.910 - 59.345, p-value = 0.007) compared to participants aged less than 26 years. Similarly, in comparisons with participants less than 26 years, respondents between the ages of 36 - 45 years were about 4 times likely to have undiagnosed hypertension (OR = 3.680, 1.263 - 10.723, p-value = 0.017) while respondents aged between 46 - 55 years old were about 3 times more likely to develop hypertension. (OR = 2.737, 1.114 - 6.727, p-value = 0.039). Furthermore, respondents aged 56 - 65 years old were about 3 times more likely to develop hypertension. (OR = 3.384, 1.610 - 7.115, p-value = 0.001).

As regards marital status participants who were married were about 4 times more likely to develop hypertension (OR = 3.846, 1.118 - 13.233, p-value = 0.033) compared to those who were single. Furthermore, as shown in Table 5(b) below, the odds for the occurrence of undiagnosed hypertension in individuals

Table 4. Association between dyslipidaemia, diabetes mellitus and hypertension.

Lipid profile	Hypertension status		Total (380)	Chi-square	p-value
	Hypertensive	Not hypertensive			
	136 (100%)	244 (100%)			
Dyslipidaemia					
Yes	89 (65.44)	106 (43.44)	195	16.916	<0.001*
No	47 (35.46)	138 (56.56)	185		
Triglycerides					
High TG	6 (4.41)	2 (0.82)	8	5.467	0.019*
Low TG/normal	130 (95.59)	242 (99.18)	372		
Low density lipoprotein					
High LDL	26 (19.12)	15 (6.15)	41	15.262	<0.001*
Low LDL/normal	110 (80.88)	229 (93.85)	339		
High density Lipoprotein					
Low HDL	79 (58.1)	101 (41.39)	180	26.451	<0.001*
High HDL/normal	57 (41.9)	143 (58.61)	200		
Total cholesterol					
High TC	33 (24.26)	6 (2.46)	39	45.085	<0.001*
Low TC/normal	103 (75.74)	238 (97.54)	341		
Diabètes mellitus					
Diabetic	18 (13.2)	13 (5.33)	31	7.288	0.007*
Non-diabetic	118 (86.8)	231 (94.67)	349		

*= Statistically significant, X^2 = Chi-square.

without dyslipidaemia was twice that of participants with dyslipidaemia R = 0.526, 0.307 - 0.902, p-value = 0.019). Factors such as occupation, level of education, religion, family history, obesity, lipid profile were not found to be independent risk factors.

4. Discussion

This study sought to determine the burden of undiagnosed hypertension in a rural community of Mbieri in Imo State Nigeria and identified a high bur den of hypertension in the study population. We identified such factors as age range 26 - 35, 36 - 45, and 46 - 55; and marital status to be independent risk factors for undiagnosed hypertension. This is the first time such a study is conducted in a rural population in Imo state Nigeria and, thus, serves as a reference point for similar studies in future.

In this study, we were able to determine the prevalence of undiagnosed hypertension as 35.8%. This is strikingly high and worrisome for a rural population, and could be the reason for the common observation at the General

Table 5. (a) Logistic regression analysis showing independent risk factors of hypertension. (b) Logistic Regression analysis showing independent risk factors of hypertension (cont'd).

(a)

Variable	Odds ratio	95% Confidence level (lower - higher)	P-value
Age (years)			
<26	1		
26 - 35	10.647	1.910 - 59.345	0.007*
36 - 45	3.680	1.263 - 10.723	0.017*
46 - 55	2.737	1.114 - 6.727	0.039*
56 - 65	3.384	1.610 - 7.115	0.001*
Level of education			
Tertiary	1		
No formal	2.764	0.191 - 39.942	0.456
Primary	0.675	0.279 - 1.637	0.385
Secondary	0.585	0.282 - 1.213	0.149
Occupation			
Farmers	1		
Professionals	0.668	0.194 - 2.299	0.523
Traders	0.731	0.179 - 2.984	0.662
C/S	1.602	0.438 - 5.858	0.476
Retired	0.737	0.207 - 2.622	0.637
Student/apprentice	1.411	0.372 - 5.353	0.613
Unemployed	0.317	0.054 - 1.855	0.202
Marital status			
Single	1		
Married	3.846	1.118 - 13.233	0.033*
Widowed	1.637	0.728 - 3.681	0.234

(b)

Variable	Odds ratio	95% Confidence level (lower - higher)	P-value
Religion			
Christianity	1		
Islam	1.127	0.379 - 3.348	0.830
Others	0.212	0.461 - 8.623	0.214
Family history			
Negative	1		
Positive	0.429	0.132 - 1.391	0.159
Not aware	1.024	0.319 - 3.285	0.968
Diabetes status			
Non-diabetic	1		
Diabetic	0.988	0.359 - 2.713	0.981

Continued

Dyslipidaemia			
No	1		
Yes	0.526	0.307 - 0.902	0.019*
Central Obesity Status (WC)			
No obesity	1		
Obesity	1.136	0.613 - 2.105	0.685
General Obesity Status (BMI)			
Underweight	1		
Normal weight	3.472	0.664 - 18.143	0.140
Overweight	1.459	0.645 - 3.300	0.364
Obesity	0.562	0.272 - 1.161	0.119
Physical Activity (PA)			
Low	1	0.099 - 1.593	0.192
Moderate	0.397	0.099 - 1.593	0.192
High	0.606	0.153 - 2.408	0.477

Out-Patient Clinics where patients often present with complication(s) of hypertension at their first encounter without any previous diagnosis. This is important for the design and development of a care plan for the rural population that incorporates their natural food and active life of farming as against the trend for unhealthy westernized diets and sedentary lifestyle, respectively. This report is similar to the results reported by Gyang *et al*. [27] in northern part of Nigeria. However, it was different from reports in other parts of Nigeria, Vincent-Onabajo *et al*., reported 25% [34] which was less while Okubadejo *et al*. reported a much higher figure of 55% [51]. The prevalence in this study was also higher than that reported from other parts of Africa by Gudina *et al*. [10], Birlow *et al*. [11], Basu *et al*. [12], Dejenie *et al*. [23], and Getachew *et al*. [24]. Another study in Poland by Szuba *et al*. [9] and Peru by Guerrero-Diaz *et al*. [17] reported a prevalence of undiagnosed hypertension to be as high as 61.7% and 67.2% respectively among the study population, which is far higher than what we found in our study. The differences could be accounted for by the differences in the study population, the age ranges chosen, and the diagnostic criteria for hypertension.

We identified such factors as certain age groups as being significantly associated with undiagnosed hypertension and were also found to be a significant risk factor. With reference to the age group of less than 26 years, those between 26-and 35 years were 10 times more likely to have undiagnosed hypertension and those between 56 and 65 years were three times more likely to have undiagnosed hypertension. This is in agreement with other studies published by Lim *et al*. [8], Dejenie *et al*. [23], Basu *et al*. [12], Bharati *et al*. [20] in their respective reports. They reported that increasing was significantly associated with hypertension. The changes associated with arterial wall compliance and arteriosclerosis, which occurs with age, in addition to less physical activity in the older, could

be a plausible explanation for this.

This study also identified marital status as being associated with undiagnosed hypertension, with being married an independent risk factor for hypertension. We found out that being married increased the risk of hypertension by four folds compared to being single. This may be due to the fact that married persons are more likely to be older, and are likely to be exposed to more psychosocial stressors. This finding is similar to what has been reported in other studies by Onwuchekwa *et al.* in Nigeria [32] and Dejenie in Ethiopia [23].

The study showed that hypertension was more common in females than males, although this was not found to be a statistically significant independent risk factor. This was similar to the reports made by Bharati *et al.* [20] where more women were found to be more likely to have hypertension, though in contrast to the reports made by Szuba *et al.* [9] and Vincent-Onabajo *et al.* [34], in their respective studies.

In addition, the study identified abnormal lipid profiles in the respondents although not as an independent risk factor for undiagnosed hypertension. The prevalence of abnormal lipid profiles was 51.3%. Similar studies by Akinlua *et al.* [16] and Oguejiofor *et al.* [52] also reported similar high prevalences of dyslipidemia among their respective study populations, and the presence of abnormal lipid profile was associated with hypertension in these studies. This association could be related to the roles abnormal lipids play in the development of atherosclerosis which will result in an increase in total peripheral resistance with attendant hypertension. Similar to abnormal lipids, obesity was common among the participants with undiagnosed hypertension but was not found to be an independent risk factor for occurrence of undiagnosed hypertension. Onwuchekwa *et al.* [32] reported similar result. This was not in tandem with most other studies as reported by Bharati *et al.* [20], Bushara *et al.* [25], Vincent-Onabanjo *et al.* [34], and Iloh *et al.* [53]. Obesity is known to be an independent risk factor for hypertension, and also associated with other risk factors of hypertension such as poor exercise. It is possible that the relatively small sample size of this study may have contributed to the inability to observe an association between abnormal lipid profile and obesity with undiagnosed hypertension in this study. Despite the well documented association between diabetes and physical inactivity with hypertension, there was no association between these factors and undiagnosed hypertension in this study, which may be related to the study site being a rural area as diabetes and physical inactivity are less common in rural areas relative to urban or developed communities.

Limitations of the Study

This study involved the collection of data of individuals in a rural community where expo sure to education and health literacy is expected to be limited. Challenges included access to the residents, and protection of the rights of the participants. Strategies applied were a meticulous informed consent process and

early interphase with the stakeholders in the community to address any concerns that the participants might have had. Secondly, this was a cross-sectional study, and the data cannot be applied in asserting a cause-effect relationship, unlike a longitudinal or experimental study. It is possible that the relatively small sample size may have yielded some false negative outcomes. In addition, random plasma lipid levels were used for analysis rather than the fasting levels which may have affected interpretation of serum triglyceride results and the conclusions therefrom.

5. Conclusion

This study revealed that the prevalence of undiagnosed hypertension in Mbieri, a rural community in Southeastern Nigeria is strikingly high. This result may not be far from what is obtainable in other rural communities in the region. Age between 26 and 36, and being married were found to be independent risk factors for undiagnosed hypertension. This study has given an insight into the burden of hypertension (and associated factors) in a rural population which is quite high. Advocacy should be sustained in the design and development of programs that will help prevent occurrence of hypertension and early detection of the disease in the community through coordinated and regular community-based health out reaches, and strengthening of the capacity of Primary Healthcare Centres which statutorily attend to the health needs of majority of populations in rural communities.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

Questionnaire

Participants serial number…

Good day Sir/Madam. This is a Questionnaire on the topic The Burden of Undiagnosed Hypertension and associated risk factors among adult dwellers of a Mbieri; a rural community in Mbaitoli LGA of Imo State. Your participation and cooperation is highly needed to carry out the study. Please fill the consent form attached to this questionnaire indicating that you are willing to participate in the study.

Using this questionnaire, the researcher will ask you some questions about your person and the disease being studied. Responses to this questionnaire will be treated confidentially. As part of the study, measurements of your blood pressure, weight, height and waist circumference will be done and your random blood glucose level and non fasting lipid profile will be determined.

Thank you for your cooperation.

SECTION A: Socio-demographic data

1) Age (in years): ☐

2) Gender: Male ☐ Female ☐

3) Level of Education: No formal education ☐ Primary ☐

Secondary ☐ Tertiary ☐

4) Occupation: Unemployed ☐ Farmer Petty trader ☐ Civil Servant ☐ Retired ☐ Student/apprentice ☐ Professional Others (Specify): ☐

5) Marital Status: Single Married ☐ Widowed ☐ Separated Divorced ☐

6) Religion: Christianity ☐ Islam ☐

Traditional Atheist Others ☐ specify ☐

SECTION B: Family history of hypertension

7) Has anyone in your family suffered from hypertension before or is there any one in your family suffering from hypertension now? Yes ☐ No ☐ Not aware ☐

8) If yes, has anyone in your family suffered from these following complications of hypertension before: Heart failure ☐ Stroke ☐ Kidney failure ☐ others (specify) ☐

SECTION C: Screening for alcohol using the AUDIT Questionnaire

1) How often do you have a drink containing alcohol (0) Never (skip to questions 9 - 10) ☐

(1) Monthly or less ☐ (2) 2 to 4 times a month ☐

(3) 2 to 3 times a week ☐ (4) 4 or more times a week ☐

2) How many drinks containing alcohol do you have on a typical day when you are drinking? (0) 1 or 2 ☐ (1) 3 or 4 ☐ (2) 5 or 6 ☐ (3) 7, 8, or 9 ☐ (4) 10 or more ☐

3) How often do you have six or more drinks on one occasion? (0)Never ☐ (1) Less than monthly ☐ (2) Monthly ☐ (3) Weekly ☐ (4) Daily or almost daily ☐

Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0

4) How often during the last year have you found that you were not able to stop drinking once you had started? (0) Never ☐ (1) Less than monthly ☐ (2) Monthly ☐ (3) Weekly ☐ (4) Daily or almost daily ☐

5) How often during the last year have you failed to do what was normally expected from you because of drinking? (0) Never ☐ (1) Less than monthly ☐ (2) monthly ☐ (3) Weekly ☐ (4) Daily or almost daily ☐

6) How often during the last year have you needed a first drink in the morning to get yourself going after a heavy

drinking session?

(0)Never □ (1) Less than monthly □ (2) Monthly

(3) Weekly □ (4) Daily or almost daily □

7) How often during the last year have you had a feeling of guilt or remorse after drinking?

(0) Never □ (1) Less than monthly □ (2) Monthly □ (3) Weekly □ (4) Daily or almost daily □

8) How often during the last year have you been unable to remember what happened the night before because you had been drinking?

(0) Never □ (1) Less than monthly □ (2) Monthly □ (3) Weekly □

(4) Daily or almost daily □

9) Have you or someone else been injured as a result of your drinking?

(0) No □ (2) Yes, but not in the last year □ (4) Yes, during the last year □

10) Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?

(0)No □ (2) Yes, but not in the last year □ (4) Yes, during the last year □

SECTION D: Screening for Physical activity using the IPAQ-SF Questionnaire.

The questions will ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the vigorous activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

1) During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ days per week _____No vigorous physical activities (skip to question 3)

2) How much time (average) did you spend doing vigorous physical activities on one of those days?

_____hours per day _____minutes per day _____Don't know/Not sure

Think about all the moderate activities that you did in the last 7 days. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3) During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____days per week _____No moderate physical activity (skip to question 5)

4) How much time did you usually spend doing moderate physical activities on one of those days? _____hours per day _____minutes per day _____ Don't know/Not sure

Think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5) During the last 7 days, on how many days did you walk for at least 10 minutes at a time? _____days per week _____No walking (skip to question 7)

6) How much time did you usually spend walking on one of those days?

_____hours per day ____minutes per day ____Don't know/Not sure

The last question is about the time you spent sitting on weekdays during the last 7 days. Include time spent at

work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7) During the last 7 days, how much time did you spend sitting on a week day?

_____hours per day _____minutes per day _____Don't know/Not sure

Section E: Clinical Measurement

Weight ……. (kg)

Height……(m)

BMI…… (kg/m^2)

Waist circumference…….. (cm)

Blood pressure …….. (mm/Hg)

Random Plasma Glucose…… (mg/dl)

Non Fasting Lipid Profile, (mg/dl) TC…… LDL……. HDL …….TG……...

THANK YOU

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