Research Article

Targeting the Warburg Effect with Glucosodiene: A Case Report of a 43-year-old Female after Mastectomy of the right breast and axillary clearance with Successful First Case Treatment for Metastatic Triple Negative Breast Cancer (TNBC) of Bone

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Breast cancer is the most common type of cancer among women, and triple-negative breast cancer (TNBC) is a particularly aggressive subtype, representing 15-20% of cases. TNBC lacks estrogen, progesterone, and HER2 receptors, making it challenging to treat. This study explores a novel approach by investigating the metabolic pathways in TNBC, focusing on the alkaline glucose isomer, glucosodiene, as a potential therapy. The Warburg effect, discovered in 1924, serves as the basis for this investigation. The case report presents a 42-year-old female patient with TNBC Patient with MRM, Modified radical mastectomy, With axillary clearance., exhibiting a right breast lump with lymph node metastasis. Diagnostic tests confirmed invasive ductal carcinoma GII with negative hormone receptors and HER2/neu. The patient had previously undergone unsuccessful traditional chemotherapy and presented with bone metastasis. Treatment with glucosodiene for 15 days resulted in normal vital functions and no signs of cellular activity. This case study aims to evaluate an individualized treatment plan for TNBC patients and establish effective follow-up protocols. The trial is registered under clinicaltrials.gov number NCT05957939.

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 doi.org/10.32388/VOB4LA

Abbreviations

- **TNBC**: triple-negative breast cancer
- **MRM**: modified radical mastectomy
- **Her2**: human epidermal growth factor receptor 2
- **BMD**: bone mineral density

1. *Background*

Triple-negative breast cancer (TNBC) is a subtype of breast cancer that lacks estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2). TNBC is considered aggressive and has a higher likelihood of recurrence than other types of breast cancer. One of the reasons for the aggressiveness of TNBC is its reliance on glucose as its primary source of energy, which is known as the Warburg effect. This reliance on glucose makes TNBC cells more vulnerable to certain treatments that target glucose metabolism, such as some chemotherapy drugs. In this context, the development of glucosodiene molecules that induce tumor hyperthermia and dissolve cancer cells from within by breaking down glucose molecules into carbon dioxide and water, generating energy that alkali elements utilize to dissolve cancer cells, has been proposed. This approach challenges the traditional notion of eliminating cancer cells and proposes using a localized concentration of alkali elements to dissolve cancer cells from within. Animal experiments and histological observations have shown the validity of this theory, and ongoing research is focused on developing new targeted therapies for TNBC. [1] [2]

Glucosodiene is an isomer of glucose that is characterized by alkaline properties. It is prepared by a substitution reaction, which is carried out by dissolving sodium bicarbonate with dextrose and heating it under certain reaction conditions to produce the alkaline glucose isomer [3]. This form of glucose is likely to inhibit glucose metabolism within the tumor, known as the Warburg effect, and may potentially limit glucose activity within the tumor, which could activate p53. Recent scientific endeavors have focused on targeting cancer through metabolic approaches, capitalizing on the altered metabolic pathways in cancer cells. Glucosodiene polymer, a newly derived compound from glucose, has shown promising results in inhibiting glucose metabolism and modifying the tumor's microenvironment acidity. The Maher Akl Theory "Glucose Mutation" proposes a strategic approach to target cancerous tumors by inhibiting glucose metabolism and altering the tumor's

microenvironment acidity using glucose isomer polymers. In this study, we investigate the effect of glucosodiene on a woman with advanced-stage breast cancer who consumed it as a dietary supplement on the development and treatment of her condition, as well as evaluate the toxicity and therapeutic activity through clinical indicators. [4]

2. *Patient information*

The patient is a 43-year-old female of white race and Arab ethnicity diagnosed with metastatic right breast cancer (invasive mammary carcinoma) that has spread to her lymph nodes and bones. She presented with a 3 cm palpable mass, pain, fatigue, and weight loss in the upper outer quadrant of her right breast, which was also detected through mammography to have spiculated and irregular borders. Her lymph nodes in the right axillary region were firm and rubbery, no previous medical history but has a positive family history of hormonal breast cancer. Treatment plans include chemotherapy, radiation therapy, and hormonal therapy.

2.1. Clinical findings timeline

The patient, a 42-year-old premenopausal woman with a positive family history of breast cancer (her mother), was diagnosed with triple-negative breast cancer (TNBC) in the right breast on **August 30, 2022**. A mammogram and ultrasound were performed on the same day, revealing a right upper quadrant asymmetry and a retro areolar thickening mass classified as BIRADS 5. The ultrasound showed infiltration of the surrounding parenchyma and metastatic lymph nodes. Figure 1

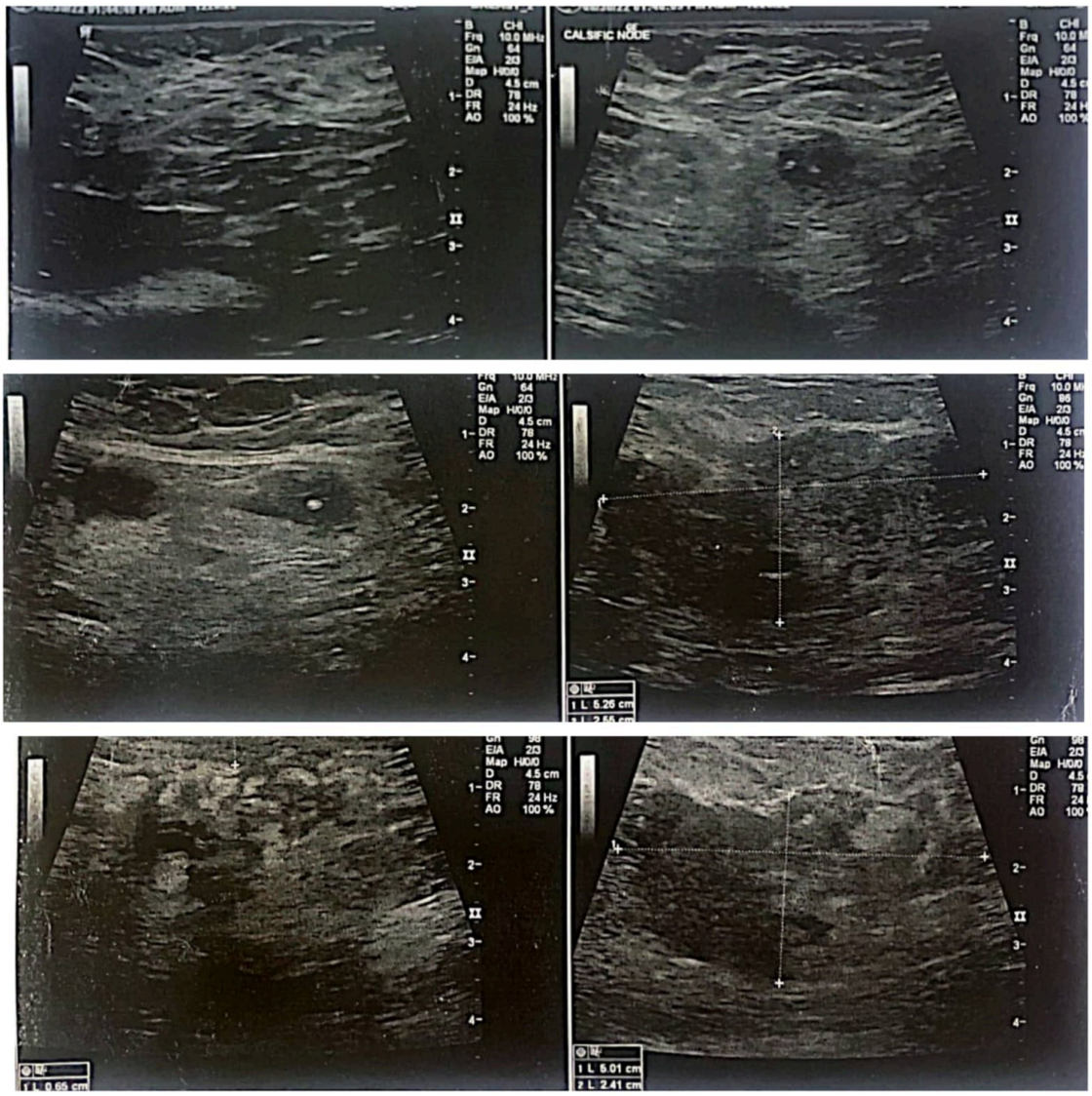

Figure 1. A mammogram and ultrasound were performed on the same day, revealing a right upper quadrant asymmetry and a retro areolar thickening mass classified as BIRADS 5. The ultrasound showed infiltration of the surrounding parenchyma and metastatic lymph nodes.

Core biopsy confirmed invasive ductal carcinoma GII with positive vascular invasion, negative estrogen receptor (ER), negative progesterone receptor (PR), and Her2/neu score 1+ negative on **September 5, 2022**. Figure 2

doi.org/10.32388/VOB4LA

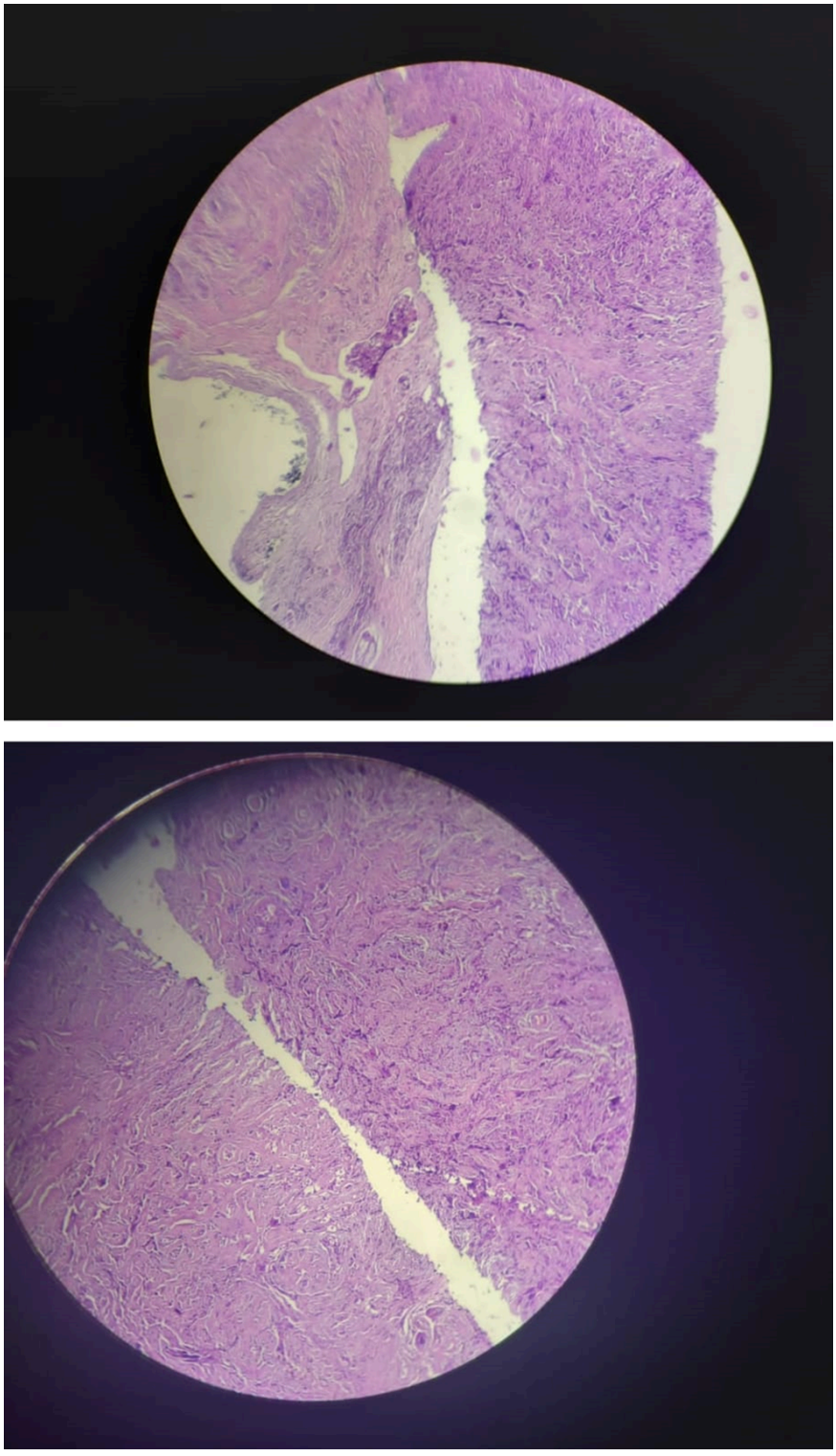

Figure 2. Core biopsy confirmed invasive ductal carcinoma GII with positive vascular invasion, negative estrogen receptor (ER), negative progesterone receptor (PR), and Her2/neu score 1+ negative.

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A metastatic workup was conducted on **September 6, 2022**, including a PET/CT scan, which showed an ill-defined infiltrative lesion in the right breast, axillary lymph node metastasis, and no clinical evidence of metastasis in the brain, neck, chest, abdomen, or pelvis.

On **March 12, 2023**, combined digital tomosynthesis, mammography, and breast sonography revealed a spiculated mass in the right breast with suspicious segmental calcifications. The patient underwent four cycles of Adriamycin and cyclophosphamide followed by 12 chemotherapy short courses with paclitaxel and carboplatin. However, on **April 1, 2023**, the tumor size returned to its original size, and aggressive recurrence occurred, causing concerns for the patient.

On **April 30, 2023**, the patient underwent a modified radical mastectomy with axillary clearance. Histopathological examination of the resected specimens revealed invasive ductal carcinoma, grade 3, with negative ER, negative PR, and Her2/neu negative (score 0).

On **June 25, 2023**, the patient experienced right leg pain, leading to a bone scan that revealed osseous metastasis in multiple areas, including the right iliac bone, head and trochanteric area of the right femur, right ischium left acetabulum, and trochanteric area of the left femur. Figure 3

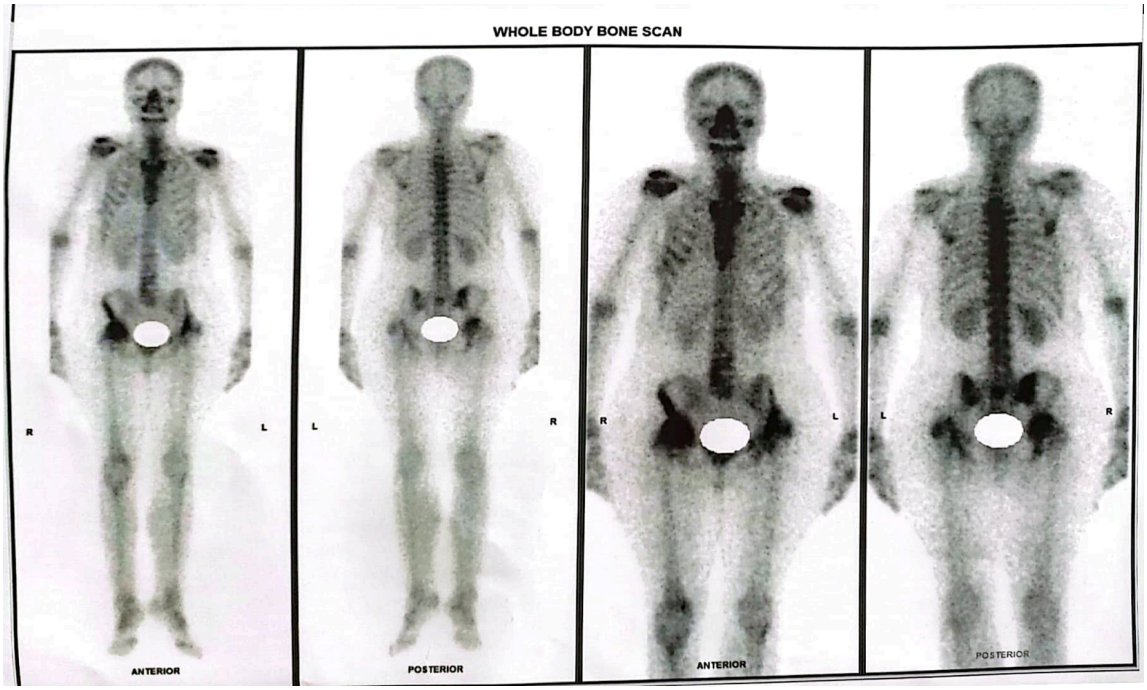

Figure 3. the patient experienced right leg pain, leading to a bone scan that revealed osseous metastasis in multiple areas, including the right iliac bone, head and trochanteric area of the right femur, right ischium, left acetabulum, and trochanteric area of the left femur.

Facing the reality of bone metastasis and fearing the future, the patient sought information and support through websites, social media, and support groups. During her research, she came across information about glucosodiene as a potential treatment targeting metabolic pathways.

2.2. Therapeutic interventions

Starting from **July 15, 2023**, the patient began taking glucosodiene as an oral supplement (100 ml) once daily at 9 pm for 15 days. Additionally, the patient adopted a low-carbohydrate diet, focusing on vegetables, proteins, and fats. After the fifth day of treatment, the patient experienced improvement and was able to walk, alleviating the severe pain in both legs following the mastectomy.

On **July 27, 2023**, an isotopic bone scan with dual-phase bone scintigraphy showed stable tracer uptake in the previously identified areas, with mild hyperemic changes during the blood pool phase. The rest of the skeleton displayed homogeneous tracer distribution without active or cold focal lesions. Follow-up bone scans were recommended. Figure 4

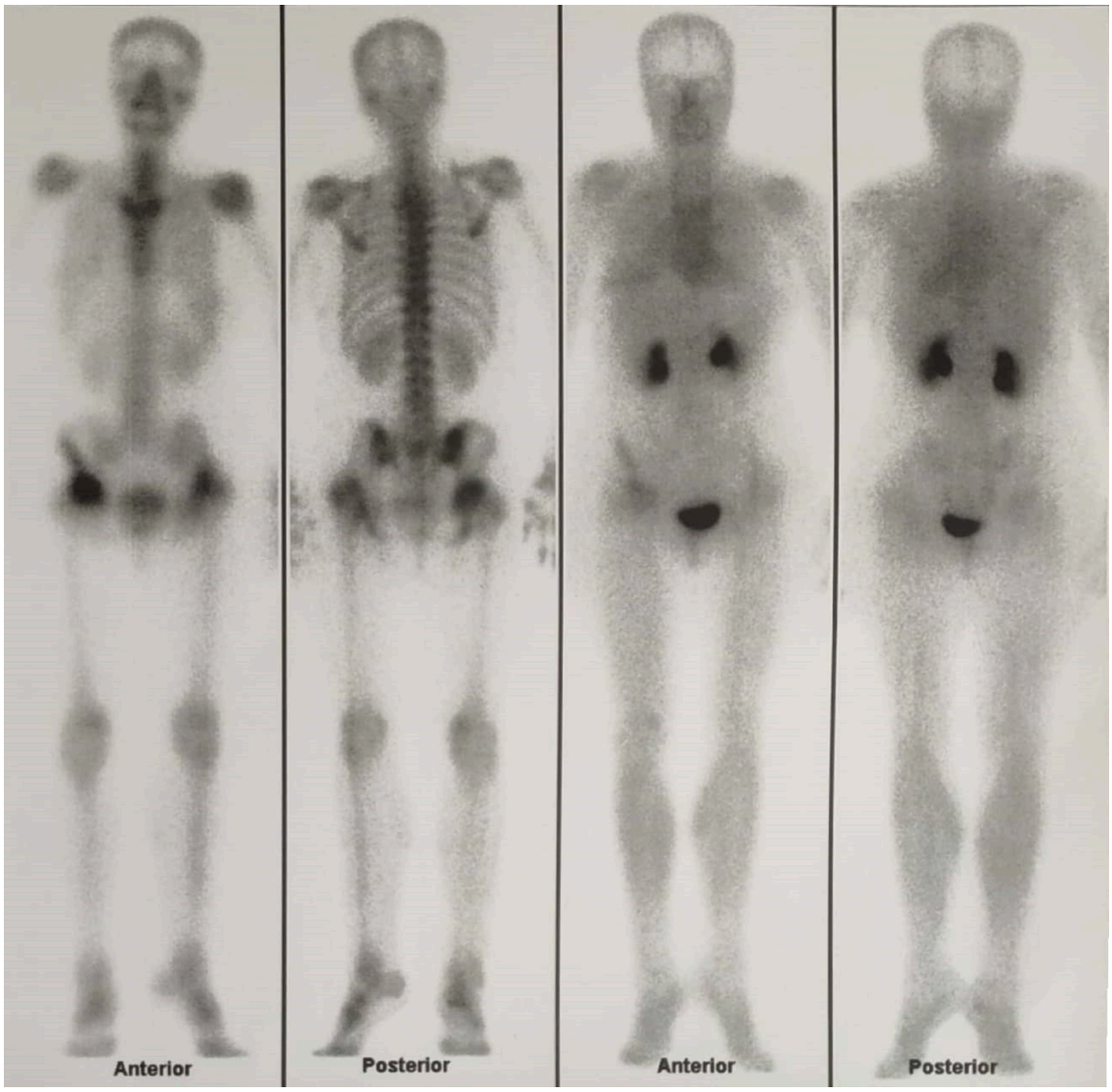

Figure 4. An isotopic bone scan with dual-phase bone scintigraphy showed stable tracer uptake in the previously identified areas, with mild hyperemic changes during the blood pool phase. The rest of the skeleton displayed homogeneous tracer distribution without active or cold focal lesions.

A DEXA scan was performed on **July 30, 2023**, to assess the patient's bone density. The results indicated low bone density and an osteoporosis diagnosis, with the left femur showing the lowest bone mineral density (BMD) measurement. The patient's fracture risk was deemed high, and treatment initiation or adjustment was recommended. Follow-up examinations after completing the treatment were advised to monitor the effectiveness of the treatment and the patient's bone health status, based on the World Health Organization (WHO) guidelines. Figure 5

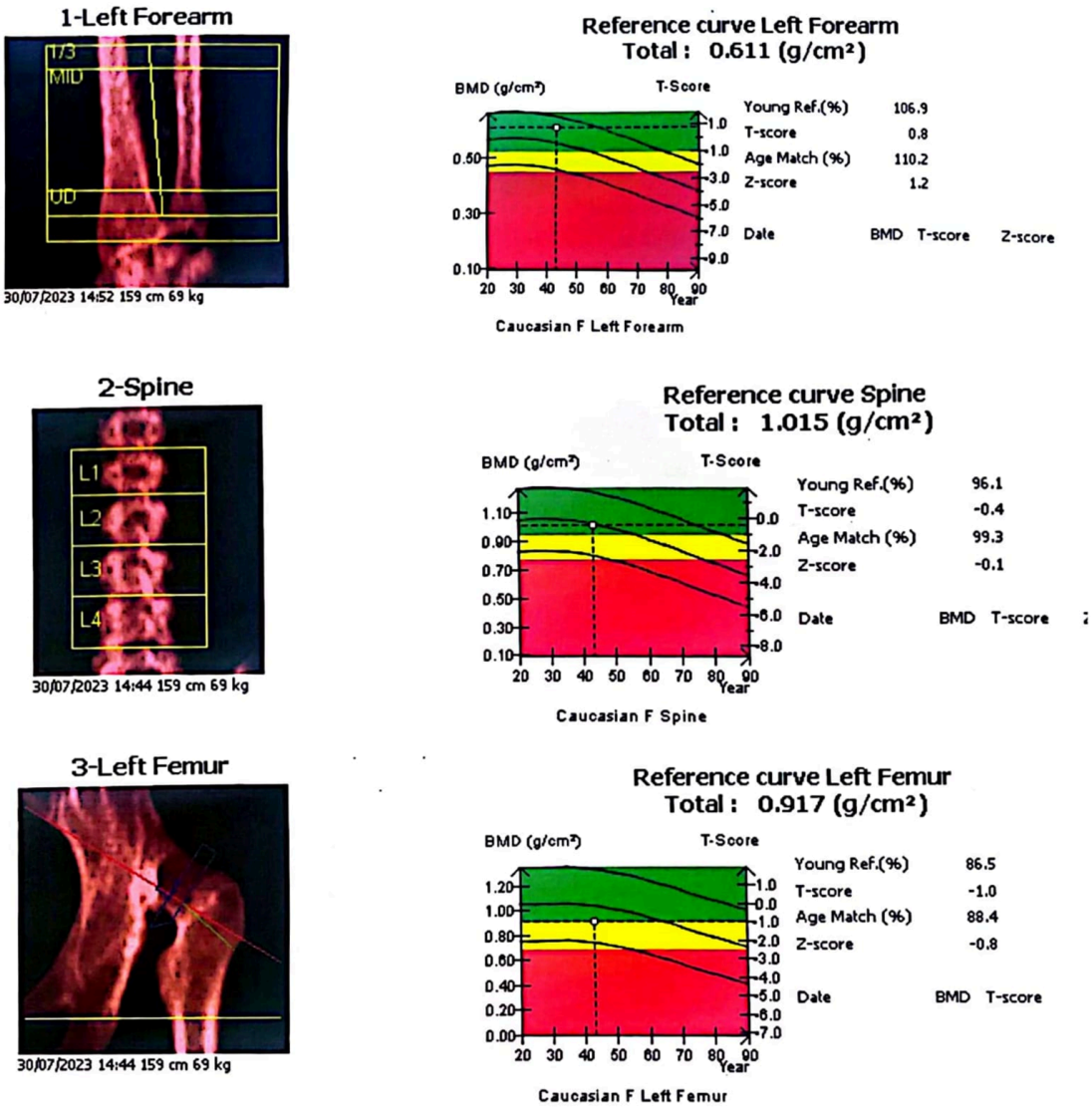

Figure 5. A DEXA scan was assessing the patient's bone density. The results indicated low bone density and an osteoporosis diagnosis, with the left femur showing the lowest bone mineral density (BMD) measurement. The patient's fracture risk was deemed high, and treatment initiation or adjustment was recommended. Follow-up examinations after completing the treatment were advised to monitor the effectiveness of the treatment and the patient's bone health status, based on the World Health Organization (WHO) guidelines.

On August 9, 2023, MRI was revealed no suspicious osseous lesions in the pelvic bone. while there were notable findings related to bilateral old developmental dysplasia of the hips (DDH) as from history taking this patient suffer from congenital hip dislocation from birth. The left hip showed

complete dislocation, while the right hip displayed marked lateral subluxation. Additionally, the right hip exhibited secondary degenerative osteoarthrosis, characterized by a flattened femoral head, subarticular sclerosis, cysts, and marrow edema. Degenerative changes were also observed at the left femoral head, along with pseudoarthrosis with the iliac bone. Furthermore, there were bilateral mild hip effusion and left iliopsoas bursitis. In summary, **the report of MRI indicated no suspicious osseous lesions in the pelvic bone** but confirmed bilateral chronic DDH with secondary degenerative changes. Figure 6

doi.org/10.32388/VOB4LA

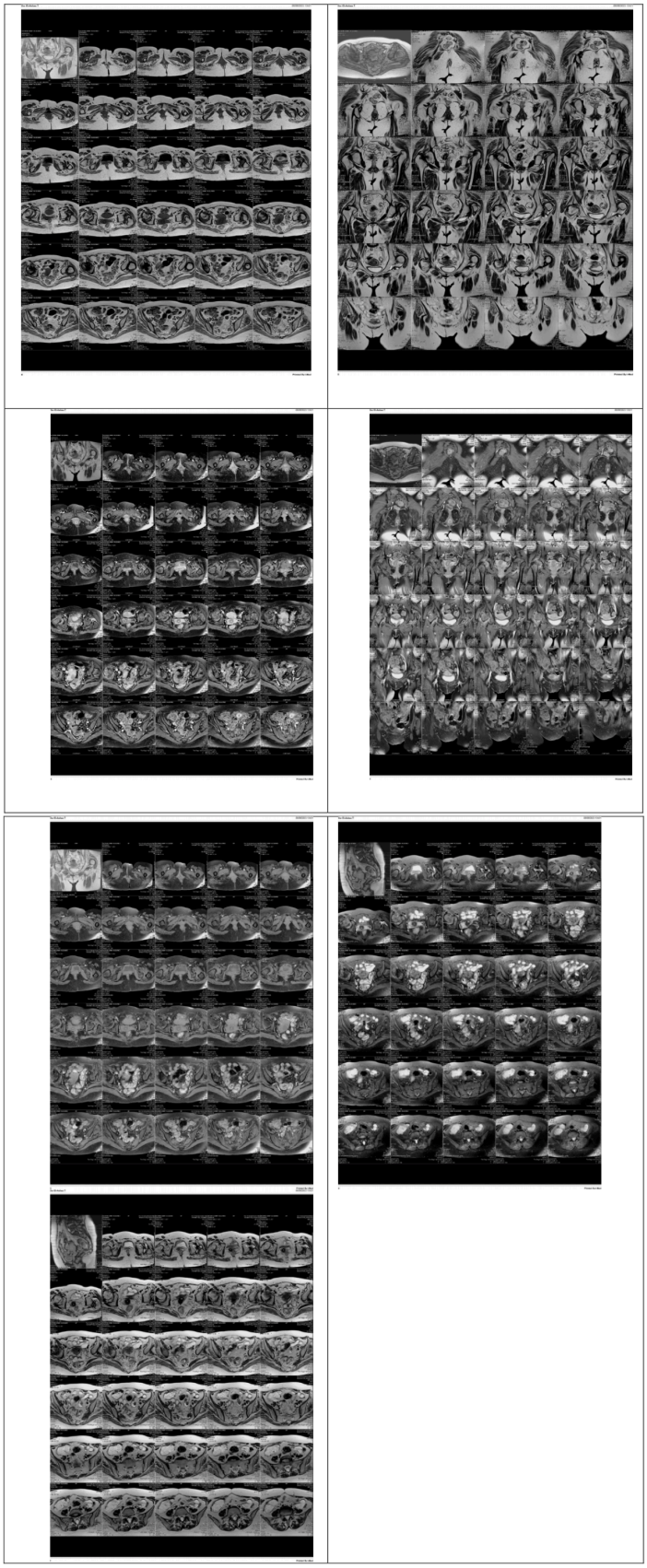

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Figure 6. MRI was revealed no suspicious osseous lesions in the pelvic bone. However, there were notable findings related to bilateral old developmental dysplasia of the hips (DDH) (the Report of MRI printed at 13 august 2023)

2.3. Vital indicators prior to treatment

Based on the results, the patient underwent medical tests (liver, kidney, heart, pancreas, blood, blood pH, and urine) before the treatment with glucosodiene on **July 15, 2023**. **The liver function** tests showed ASGOT (Aspartate Aminotransferase) levels of 26 U/L (Reference Range: Up to 40 U/L) and ASGPT (Alanine Aminotransferase) levels of 22 U/L (Reference Range: Up to 45 U/L).

The kidney function tests revealed a serum creatinine level of 0.75 mg/dL (Normal: 0.6-1.4 mg/dL) and a blood urea level of 34 mg/dL (Normal: 15-45 mg/dL). **The cardiac marker**, ALDH (Lactate Dehydrogenase), was measured at 393 U/L (Normal: 230-460 U/L). In **the hematology report**, the patient had a hemoglobin level of 12.8 g/dL (Reference Range: 11.7-15.5 g/dL), a red blood cell count of 4.45 x 10^3 Cells/μL (Reference Range: 3.8-5.1 x 10^3 Cells/μL), and a hematocrit level of 42.6% (Reference Range: 35-45%). The platelet count was 181 x $10^3/mm^3$ (Reference Range: 150-440 x $10^3/mm^3$), and the white blood cell count was 8.93 x $10^3/mm^3$ (Reference Range: 4.5-11.0 x $10^3/mm^3$). **The urine examination** showed normal physical properties, including random volume, amber-yellow color, aromatic odor, and deposit aspect. **The chemical examination** revealed an acidic pH of 5.5, negligible trace protein, absence of sugar, acetone, nitrite, and bilirubin, and normal urobilinogen levels. Leukocytes and blood were absent. **The microscopic examination** showed 4-6 pus cells/HPF (High Power Field), 2-4 RBCs/HPF, few epithelial cells/HPF, absence of casts, calcium oxalate crystals (++), and no ova, trophozoites, mucus, or fungi. These results indicate that the vital indicators are within the normal range.

2.4. Vital indicators after treatment

Based on the results of the medical tests conducted after receiving glucosodiene treatment on **July 20, 2023**, the patient's **liver functions** were within the normal range. The SGOT (Aspartate Aminotransferase) level was 32 U/L (up to 40 U/L), and the ASGPT (Alanine Aminotransferase) level was 26 U/L (up to 45 U/L). The ALP (Alkaline Phosphates) level was 164 U/L (normal: 40-100 U/L), and the AGGT (G-Gutamyl Transpeptidase) level was 23 U/L (normal: 7-40 U/L).

The kidney functions were also normal, with a serum creatinine level of 0.9 mg/dL (normal: 0.6-1.4 mg/dL) and a blood urea level of 24 mg/dL (normal: 15-45 mg/dL).

The cardiac markers showed a lactate dehydrogenase (LDH) level of 458 U/L (normal: 230-460 U/L).

In **the hematological report**, the blood picture showed a hemoglobin (Hgb) level of 12.2 g/dL (reference range: 11.7-15.5 g/dL), a red blood cells (RBCs) count of 4.52 x 10^6 cells/pl, and a hematocrit (Hct) level of 42.3% (reference range: 35-45%). Other parameters such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and white blood cells (WBCs) count were also within the normal range.

The urinalysis report indicated normal physical examination findings, including volume, color (amber-yellow), odor (aromatic), turbidity (absent), aspect (clear), and deposit (absent). The chemical examination showed an acidic pH of 6.5, negligible trace protein, and absence of sugar, acetone, nitrite, bilirubin, and urobilinogen. Leukocytes and blood were also absent. The microscopic examination revealed a few pus cells, no red blood cells (RBCs), epithelial cells, casts, crystals, ova, trophozoites, mucus, urine artifacts, fungi, or bacteria.

The coagulation profile showed a D-dimer level of 0.42 mg/L (normal: 0-0.50 mg/L), and the serum electrolytes indicated a phosphorous level of 4.58 mg/dL (normal: 2.5-5.0 mg/dL). The venous blood pH was 7.33 (normal: 7.4).

Based on these results, there were no signs of cellular toxicity or impairment in vital body functions after glucosodiene treatment. The liver, kidney, heart, pancreas, blood, blood pH, and urine were all within the normal range, indicating the safety of glucosodiene.

3. *Discussion*

This study presents a case report of a 42-year-old female patient with advanced-stage triple-negative breast cancer (TNBC) stage 3 that had metastasis to the lymph nodes and bones. The patient had previously undergone unsuccessful traditional chemotherapy (4 cycles of Adriamycin and cyclophosphamide every 3 weeks and 12 cycles weekly of Paclitaxel and carboplatin and then go forward directly to surgery with modified radical mastectomy (MRM) then patient suffered from severe pain in the pelvis and legs so admit at the hospital for a bone scan which was revealed many hot active sites uptake refers to osseous metastasis in multiple areas, including the right iliac bone, head

and trochanteric area of the right femur, right ischium left acetabulum, and trochanteric area of the left femur. In-vitro study's discussed the role of high glucose environment at different concentrations of zinc and in the presence or absence of insulin or interleukin 6, the study showed that in the presence of insulin resistance Notably, the expressions of ZnT1, ZnT5, ZIP6, ZIP7, ZIP10, and ZIP14 significantly increased when Zn was increased from 10 M to 100 M under high glucose conditions. Additionally, the relative expression for ZnT1 and ZIP10 reached values well above 20-fold. [5] so the glucose environment favors the invasion and metastasis behavior of triple-negative breast cancer also in the presence of increased zinc. After MRM the patient stopped all medicines and finished all chemotherapy cycles so she thought to take glucosodiene, an alkaline glucose isomer, as a dietary supplement. Then she is followed by our team, The initial five days of treatment with glucosodiene resulted in an improvement in the patient's general health, and able to walk after bed rest for many weeks after surgery and take many analgesics daily to overcome pain, improved of the patient was further confirmed by laboratory tests indicating the health and effectiveness of her vital organs. This suggests that glucosodiene may have a positive impact on the treatment of TNBC. The mechanism of action of glucosodiene in treating TNBC can be attributed to two possibilities. First, glucosodiene may inhibit the GLUT1 receptors, as previous studies have shown that GLUT1 inhibition blocks the growth of RB1-positive triple-negative breast cancer. Second, modifying glucose to an alkaline form may impede glucose metabolism within the tumor, known as the Warburg effect. One century after the discovery of the Warburg effect, in the 1920s that tumors absorbed huge amounts of glucose in comparison to surrounding tissue. Furthermore, even in the presence of oxygen, glucose was digested to create lactate, giving rise to the phrase aerobic glycolysis [6]. As the metabolic pathway is the hallmark of triple-negative breast cancer recently scientists have focused on the role of the metabolic pathway and zinc transporters as studies by Takatani-Nakase T et al showed that Zinc and its transporters, ZIP6 and ZIP10, are essential for glucose-stimulated motility.[7]

These findings provide the first evidence for novel techniques for the detection and treatment of hyperglycemia-related breast cancer. Disrupting the tumor's glucose metabolism could potentially reactivate the p53 enzyme, which is known to influence glucose flux and regulate glycolysis. [8] Furthermore, the alkaline nature of glucosodiene may disrupt the tumor's microenvironment without affecting healthy cells, as evidenced by the safety of vital organ indicators such as the kidney, liver, heart, and blood pH. After 15 days of treatment with glucosodiene, the patient underwent bone scanning, which revealed no presence of active or cold foci. MRI was revealed no suspicious osseous

lesions in the pelvic bone. This finding suggests the effectiveness of glucosodiene in stopping and controlling the activity of metastatic triple-negative breast cancer in the advanced stage. But one case is not enough to give the efficacy of this drug and needs more clinical studies regarding metastatic triple-negative breast cancer.

4. *Conclusion*

This case study highlights the potential efficacy of glucosodiene as a therapeutic approach for advanced-stage triple-negative breast cancer. The alkaline glucose isomer may interfere with glucose metabolism and reactivate key enzymes involved in tumor control. Further research and clinical trials are warranted to evaluate the effectiveness and safety of glucosodiene as a targeted therapy for TNBC patients.

Statements and Declarations

Informed consent: Before taking this case, information was given to the patient and informed consent was obtained from the patient for follow-up and consent to share the investigations and figures and any required data.

Funding information: The authors received no financial support for the research and publication of this article

Competing interest declaration: The authors declare that there are no conflicts of interest.

Ethical approval statement or statement of informed consent for case studies: this case was conducted in accordance with the declaration of Helsinki and met the **CARE guidelines** criteria and informed consent was obtained from the patient for follow up including permission for publication of all photographs, lab, and images herein.

Clinicaltrials.gov registration details number: NCT05957939

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Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.