Article

Transglutaminase 1 Activity in Brain Cancer Patients and Healthy People

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Abstract

Cancer is defined as a group of abnormal cells that grow and spread unusually, and sometimes their proliferation cannot be controlled. These tumours are usually called cancer. Cancer may affect damaged parts of the body, including the brain. This study focused on the activity of transglutaminase 1 in the blood serum of brain cancer patients and then compared it with the control group. The study also included the effect of age, gender, body mass index, and glucose on the transglutaminase 1 in the blood serum of patients with brain cancer. The study sample consisted of 45 samples of brain cancer patients, (45) samples as a control group. The results showed a significant decrease in the activity of transglutaminase 1 in brain cancer patients (902.66 ± 14.27 ng/L) compared to the control group (1594.66 ± 32.95 ng/L). Gender and age also impact the enzyme; in the control group only, males had lower enzyme activity than females, and the enzyme's activity decreased with age in both groups (brain cancer patients and controls). The findings also demonstrate that there was a discernible difference in the serum glucose concentration of brain cancer patients when compared to the control group, although it was still within normal allowable limits, and that there was a decrease in the enzyme's activity with an increase in body mass index values

in both the patient and control groups. The investigation of transglutaminase 1 is a useful marker for identifying brain cancer and can be utilized in early diagnosis.

Keywords: Cancer, Transglutaminase 1, Body Mass Index, Glucose, Brain

Introduction

"cancer" refers to diseases caused by the body's abnormal cells proliferating and spreading uncontrollably [1]. Cancer, or tumours, is a general term for diseases caused by abnormal cells in the body that develop and spread uncontrollably [2]. Every year, the number of cancer cases rises as a result of pollution in the air, water, and land, as well as the introduction of canned goods without proper quality control [3]. Some of the symptoms of brain tumors are headaches, seizures, memory or cognitive impairments, visual or hearing alterations, balance problems, and behavioral or personality changes [4]. Treatment options for brain tumors vary depending on the kind, size, location, and general health of the patient. MRIs and CT scans, which are commonly used to identify the type of tumor and its features, are also sometimes combined with a biopsy to confirm the diagnosis [5]. Surgery, radiation therapy, chemotherapy, targeted medication therapy, or a mix of these may be used as a form of treatment [6]. An enzyme known as transglutaminase 1 (TGM1) is essential to the keratinization process, which creates the epidermis, the skin's protective outer layer. This enzyme is especially crucial for the formation of the epidermal barrier, which shields the body from contaminants, dehydration, and infections [7]. This enzyme belongs to a family of enzymes that are vital to many biological processes, such as tissue repair, wound healing, and blood clotting [8]. The body has many forms of transglutaminases 1, including the brain [9]. According to a study, transglutaminases may contribute to the development of cancer, especially brain tumors (BT) [10]. Gliomas are among the many forms of brain tumors that express TGM1. Through the promotion of protein cross-linking within the tumor microenvironment, TGM 1 can aid in the development and spread

of tumors. Proteins involved in cell adhesion, migration, and invasion-all of which are essential for the advancement of cancer—can be stabilized by this process [11]. Transglutaminases have been investigated as possible therapeutic targets for the treatment of cancer, especially brain tumors, due to their role in supporting cancer cell survival and metastasis. Transglutaminase activity inhibition may interfere with these functions and prevent tumor growth [12].

Since there isn't much information on the assay of transglutaminase 1 in blood serum, due to the paucity of biochemical research on the correlation between transglutaminase 1 and brain cancer, particularly in light of the rise in brain cancer cases in Iraq, the study's main goal was to measure the level of transglutaminase 1 activity in the blood serums of patients with brain cancer and healthy individuals, as well as the relationship between the two.

Material and Methods

Chemical and standard kits

Every chemical and standard utilized in this investigation for analytical reasons was used with a high-purity

Research procedures

The scientific committee of Tikrit University's College of Science approved the study's protocol. On April 5, 2023, during its 242nd session, the Scientific and Ethical Research Committee of the Nineveh Health Department also approved the study's conduct and provided the necessary data and samples.

45 individuals with brain cancer are included in this research. Samples were taken from patients receiving treatment at the Mosul Oncology and Nuclear Medicine Hospital in Mosul, Iraq, between April and September of 2023. Each case's clinical diagnosis was determined based on the oncologist's recommendations. The ages of

each patient ranged from 9 to 76. The study's participants had been diagnosed with brain cancer both clinically and histologically, and they had no history of diabetes, hypertension, or other chronic illnesses affecting the heart, kidneys, or liver. The female cases weren't nursing or pregnant. The control group was made up of forty-five normal, healthy people who were matched in age to the patients and had no evidence of any benign or malignant brain disease. They also showed no indications or symptoms of cancer or chronic illnesses.

Blood Sample Collection

Samples of venous blood were taken following an overnight fast. Venous blood samples of 8 ml were collected from both patients and control samples 2 ml. of fresh venous blood was preserved right away in a tube which contained an anticoagulant. The remaining blood was then allowed to clot in a gel tube for fifteen minutes at room temperature to obtain blood serum.

Human Transglutaminase 1 Determination

TGM 1 is a serum of Transglutaminase 1 activity, which was determined using a kit assayed according to the manufactured procedure (Bioassay Technology Laboratory, Cat. No. E6023Hu, Shanghai, China). The Detection Range is 15-3000 ng/L, and the sensitivity is 7.03ng/L.

Assay Principle

This work employed a precise quantitative sandwich enzyme immunoassay approach to detect human Transglutaminase 1 (TGM1). The plate was pre-coated with a human TGM1 antibody (Human Protein-glutamine Gamma-glutamyltransferase, TGM1). Then, TGM1 (the Antigen) from the sample was added, which binds to antibodies coated on the wells. A biotinylated Human TGM1 Antibody was also added, which binds to TGM1 from the sample.

Next, the biotinylated TGM1 antibody bound streptavidin-HRP. After incubation, unbound Streptavidin-HRP was eliminated in a washing phase. Subsequently, the hue changed in direct proportion to the concentration of Human TGM1 when the substrate solution was introduced. At 450 nm, absorbance was measured, and an acidic stop solution was added to halt the process.

Calculation of Body Mass Index (BMI) using Weight and Height Measurements

Trained nurses measured each participant's height (cm) and weight (kg). The subjects were dressed comfortably and barefoot when their body weight was assessed using a balancing scale. The balance scale was set to the nearest half-kilogram. Weight in kg divided by height in meters squared yields the BMI, or Quetelet index. The next equation is used to calculate BMI

$$\text{Body Mass Index} = \frac{\text{weight (kg)}}{\text{height (m}^2\text{)}}$$

The following ranges represent the BMI classifications used by the WHO: Underweight is defined as 18 or less, ideal weight as 18.5-24.9, overweight as 25-29.9, and obesity as 30 or more. [13].

Serum Glucose Determination

The solutions were placed in three test tubes: the sample, the standard (glucose), and the blank. After mixing the solution tubes and incubating them at 37 °C for five to ten minutes, the absorbance (A) of the samples and the standard were measured at 505 nm using a spectrophotometer (PYE-UNICAM, U.K.)

Statistical analysis

The ready-made statistical program SPSS 22 (SPSS Software, SPSS Inc., Chicago, Illinois, USA) was used to analyze the data [14]. All results were presented as the

average ± standard deviation. to compare the relevance of the various categories. To identify any significant differences between the research groups, the findings were statistically evaluated using the t-test and the correlation coefficient. A probability level of $p < 0.05$ was deemed significant, while $p>0.05$ was deemed non-significant. Pearson's correlation is used to ascertain whether the variables under study have an effective connection.

Results and Discussion

The activity of TGM 1 in the blood serum of the control group was found at 15.94.66 ± 32.95 ng/L for both genders, as presented in **Table 1**.

Adults typically use a reference range of less than 4 U/mL. A result of more than 4 U/mL in children is very indicative of celiac disease, and in certain circumstances, this may mean that a biopsy is not necessary. [15,16]. For the patient group, it has been found that the activity of TGM 1 in the serum of both genders and for ages (9-74 years), was (902.66± 14.27 ng / L) (**Table 1**).

Table (1): Activity of serum Transglutaminase 1 for both control and patients

Age groups	Transglutaminase 1 activity (ng/L) (mean ± SD)					
	Control group (n=45)			Patients group (n=45)		
	Males (n=23)	Females (n=22)	Total	Males (n=23)	Females (n=22)	Total
(9-29) years (N=13)	1499.56 ± 29.13 **c**	1881.47 ± 30.21 **g**	1710.02 ± 28.55 **f**	946.15 ± 26.36 **c**	1089.63 ± 27.91 **g**	1012.52 ± 17.25 **e**
(30-59) years (N=16)	1401.55 ± 16.85 **b**	1748. 42± 22.45 **f**	1574.17 ± 21.35 **d**	901.41 ± 11.85 **b**	1047. 82± 32.45 **f**	974.99 ± 25.15 **d**
(60-89) years (N=16)	1264.76± 21.73 **a**	1624.11 ± 13.87 **e**	1444.43 ± 18.18 **bc**	854.46 ± 18.18 **a**	1001.18 ± 18.07 **e**	927.53 ± 27.12 **bc**
Total mean	1444.96 ± 19.90 **bc**	1754.12 ± 23.05	1594.66 ± 32.95 **d**	884.82 ± 22.14 **a**	1034.12 ± 11.35 **F**	902.66± 14.27 **b**

		f				

a, b, c, d, e, f & g infer that the means significantly differ at P≤0.05 among the groups of studied.

Impact of genders according to age on TGM 1 activity in the blood serum

On control group:

It investigated how gender affected the level of TGM1 activity in the control group's serum based on age. The blood serum of the control group for the first age group compared with the older age groups indicates a reduction in TGM1 activity with an increase in age of both genders (P≤0.05). Transglutaminase 1 activity was significantly lower in men than in females across all age groups when comparing the sex of the individuals. This finding is similar to [17], indicating that TGM1 activity was lower in males than in girls. Male and female variations in transglutaminase 1 activity can be ascribed to several physiological and biological variables. Research on transglutaminases and enzyme activities in different sexes provides insights, even if the specific research results did not directly address variations in TGM1 activity.

There are some factors that can affect TGM 1 activity, such as hormonal influence: Sex hormones, particularly androgens and estrogens, significantly influence enzyme activities [16]. Higher testosterone levels in men are often associated with enhanced enzyme activity and specific metabolic pathways. On the other hand, transglutaminases' expression and activity may be affected by the increased estrogen levels in females. The interaction of hormones may cause differences in TGM1 activity between both genders. Muscle and Tissue Composition: Studies show that men typically have more muscle mass and a distinct makeup of muscle fibers than women. This has the potential to impact the production and function of muscle-related enzymes, such as transglutaminases [18], and it may also be significantly influenced by genetic, epigenetic, and gender-specific variables [18].

On patients group

In a study examining the impact of sex and age on enzyme activity in the serum of brain cancer patients, significant decreases in Transglutaminase 1 activity were observed with advancing age for both females and males, with a probability level of $P \leq 0.05$. This finding suggests that age significantly influences enzyme activity. Recent research highlights the importance of Transglutaminase 1 in various biological processes, such as cell differentiation and tissue repair, and indicates that its activity may reflect underlying pathophysiological conditions. The findings suggest that one important factor influencing TGM1 activity is age. This enzyme's activity decreases with age in patients, which might have an impact on how well their condition progresses and how well their treatments work. Even while TGM1 activity decreased with age in both sexes, the results may also call for more research to see if the pace or degree of this reduction differs in males and females [17]. Understanding these differences may facilitate more personalized treatment and management strategies for brain cancer. Research indicates that several enzymes in brain cancer patients, including Transglutaminase 1, significantly decline activity with age. Here are some notable examples:

Indoleamine 2,3-Dioxygenase: its expression increases with age; however, its enzyme activity does not rise similarly. This suggests a potential decline in functionality despite higher expression levels. This discrepancy prompts further investigation into IDO1's role in immunosuppression and its effects on brain cancer outcomes in older patients [19, 20]. Catalase: Like Se-GPx, catalase activity has been shown to decrease in patients with brain cancer. This enzyme is crucial for breaking down hydrogen peroxide, and its diminished activity can result in increased oxidative stress, which may exacerbate cancer pathology [21].

Acetylcholinesterase (AChE) activity is significantly impaired in cancer patients, including those with brain tumors. This impairment can result in elevated acetylcholine levels, potentially influencing tumor growth and aggressiveness [22].

The decline in TG1 activity with age may serve as a potential biomarker for evaluating disease severity or progression in brain cancer patients. Additionally, understanding the effects of age and sex on enzyme activity could aid in developing tailored therapeutic strategies that are age-appropriate and sex-specific.

Impact of BMI (Body Mass Index) on TGM 1 activity in the blood serum

On control group

The formula for calculating BMI is weight divided by height. According to WHO criteria, BMI is categorized as follows: BMI less than 18.50 indicates underweight; 18.5 ≤ BMI less than 25.0; 25.0 ≤ BMI less than 30.0; and BMI more than 30 indicates obesity [23]. As can be seen in Table (2), the control group was split into two groups based on body mass index (BMI) since an increase in BMI is associated with a substantial decrease in TGM 1 activity at the probability level ($P \leq 0.05$). To recognize the connection between body mass index and transglutaminase 1 activity. It noted that TGM1 activity has been found to decrease significantly with rising BMI; this suggests that TGM1 activity decreases with rising BMI and that the association is statistically significant.

The production of covalent connections between proteins, which is necessary for the structural integrity of tissues, is one of the many biological processes in which the enzyme TGM1 plays a critical role. The reduction in TGM1 activity with rising BMI may be due to several processes, including inflammatory cytokines. Increased levels of inflammatory markers are frequently linked to higher BMIs, and this may limit TGM1 function. alterations in dietary and hormonal aspects as well [23].

The substantial decline in transglutaminase 1 activity with rising BMI draws attention to a crucial field of study that may be useful in understanding health problems associated with obesity. To lessen the side effects linked to decreased TGM1 activity, further research is required to investigate the underlying processes and possible treatment targets [24].

Table (2): Impact of BMI on TGM1 activity in the serum in both groups

Groups	BMI (kg/m²)	TGM1 (ng/L) (avarage ± SD)
Control group	Normal (≤ 25)	1758. 62± 21.95 a
	Obese (≥ 30) (n=21)	1294.86 ± 31.13 b
Patient group	Normal (≤ 25)	959.93 ± 8.19 a
	Obese (≥ 30) (n=40)	900.03± 24.12 b

a & b infer that the average is significantly different at P≤0.05 among the groups studied.

On patients group

Table (2) shows that a significant drop in the probability level (P≤0.05) in enzyme activity is detected with an increase in the BMI in the patient's blood serum. The patients were classified into two groups based on their BMI.

High BMI (overweight or obese) has been linked to several disorders [25, 26] and has been linked to several negative health and financial effects, including greater yearly medical care expenses [27] and increased mortality and morbidity.

Numerous epidemiological studies have connected obesity to a higher risk of brain tumour development, including gliomas and meningiomas. Obesity has been linked to an increased risk of meningiomas, gliomas, and brain/CNS cancers, according to a meta-analysis [28]. A different meta-analysis revealed a correlation between an elevated BMI and physical activity with a greater risk of adult meningioma and glioma [29]. A 7% higher cancer risk, including brain cancer, has been linked to

obesity in men [30]. Although the precise processes relating obesity to the risk of brain cancer are not entirely known, they may include obesity-related variables such as insulin resistance and elevated inflammation [31].

Effect of Glucose on TGM 1 activity in the blood serum

Those suffering from brain cancer had noticeably increased blood glucose levels (102.36±1.06 mg/dL), compared with those of the control (91.20±0.97 mg/dL), P<0.05 **Figure (1).** There is a relationship between glucose levels and brain cancer; some studies link hyperglycemia to increased brain cancer risk and aggressiveness. It can be explained by reduced insulin production, aberrant glucose tolerance, or insulin resistance (along with compensatory hyperinsulinemia). Given that insulin is known to have a role in cell differentiation, aberrant insulin activity may be a sign of an increased risk of cancer cells growing undifferentiated [32, 33].

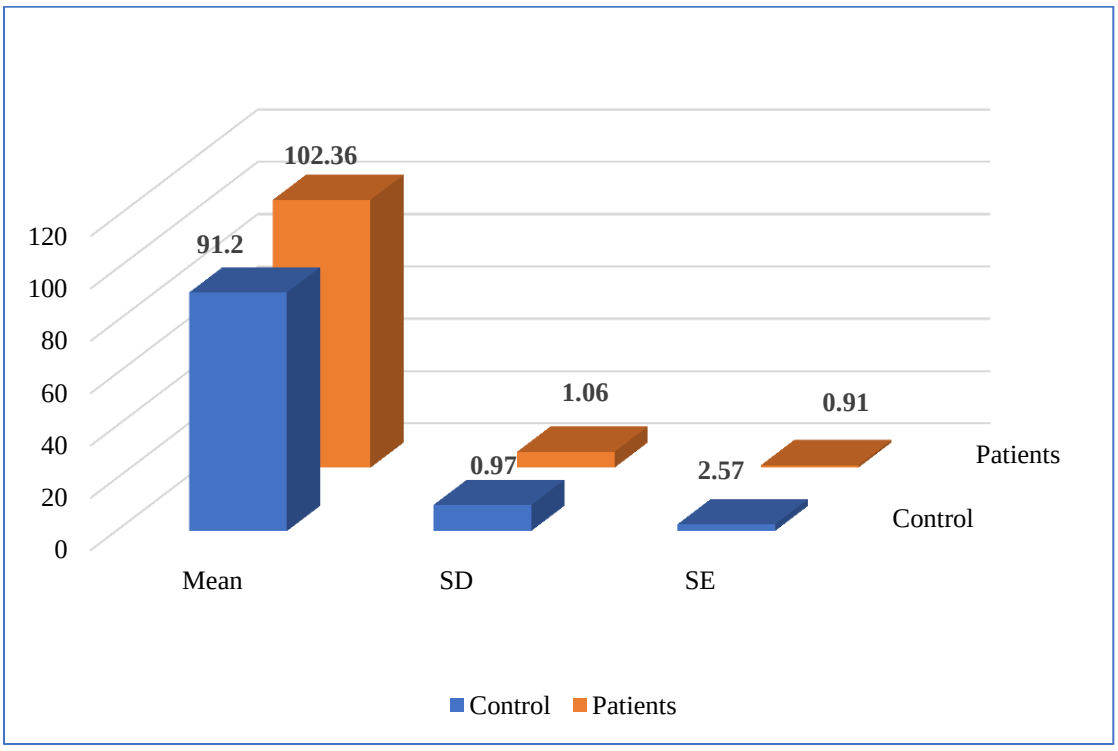

Figure (1): Glucose concentration (mg/dl) in brain cancer patients and control groups

Conclusions

Transglutaminases are a family of enzymes that play diverse roles in different biological processes. It is expressed in various tissues, including the brain. In the case of brain cancer, such as gliomas, researchers have explored its activity and potential impact. This study determined the activity of TGM 1 enzyme in brain cancer patients' blood serum and compared this activity to the control group (healthy people). The impact of age, gender, body mass index, and glucose on the transglutaminase 1 enzyme in brain cancer patients' blood serum was also examined in this study. The results revealed that significant decrease in the activity of transglutaminase 1 in brain cancer patients compared to the control group. In addition, the results revealed that transglutaminase 1 activity decreased with age and increased in body mass index. Finally, transglutaminase 1 is considered a useful biomarker for the early detection of brain tumours. The researchers recommended an additional investigation to evaluate the activity of transglutaminase 1 in brain tumour tissues from brain cancer patients.

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