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Study of the association between GLIS3 rs10758593 and type 2 diabetes mellitus in Egyptian population

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Abstract

Background: GLIS3 (Gli-similar 3), a transcription factor, is involved in the maturation of pancreatic beta cells in fetal life, maintenance of cell mass as well as the control of insulin gene expression in adults. As a result, GLIS3 was reported as a susceptibility gene for type 1 diabetes, type 2 diabetes, and neonatal diabetes. Therefore, the goal of this study was to look into the association between the rs10758593 single nucleotide polymorphism (SNP) in the GLIS3 gene and T2DM in the Egyptian population.

Methods: Frequencies of the rs10758593 (A/G) SNPs were determined in 100 T2DM patients (cases) and in 100 non-diabetic healthy subjects (controls) using real-time PCR.

Results: The prevalence of the mutant genotypes, AA and AG, differed significantly between patients and controls. The AA genotype was more prevalent in the patients' group. The (AA) was found in 39% of the patients and 18% of the controls. While AG (heterozygous) genotype was found in 61% of the patients and 81% of the controls ($p = 0.003$). The AA genotype was significantly associated with T2DM. Moreover, The GLIS3 rs 10758593 mutation was found to be associated with the presence of diabetic retinopathy and nephropathy. In diabetic patients, a significant correlation between HbA1c with fasting glucose, fasting insulin, and HOMA-IR was found.

Conclusion: The rs10758593 polymorphism of the GLIS3 gene was found to be significantly associated with T2DM in an Egyptian population sample. Additionally, significant association between GLIS3 rs 10758593 mutation and the glycemic control was found.

Keywords: T2DM, GLIS3, Gene polymorphism, Diabetic retinopathy, Diabetic nephropathy

Background

Diabetes mellitus (DM) is a significant health-care burden worldwide. By 2030, the World Health Organization predicts it will be the seventh largest cause of mortality [1]. Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes mellitus, accounting for around 90% of all diabetic cases [2]. Egypt has the ninth highest diabetes incidence rate in the world, with up to 8.9 million individuals afflicted, according to the International

Diabetes Federation (IDF). Due to its fast expanding and ageing population, Egypt is predicted to rank seventh by 2045, with about 16.9 million diabetes patients, the highest prevalence in the Middle East and North Africa [3]. T2DM is considered to be a polygenic disease produced by the interplay of many genes as well as environmental and lifestyle variables [4]. Several genes have been identified in studies that may be linked to T2DM, including the GLIS3 gene [5].

GLIS3 is a transcription factor from the Kruppel-like zinc finger family that is prevalent in beta cells, thyroid, and kidney. GLIS3 is a transcription factor that regulates

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insulin gene expression in adults and cell mass maintenance, as well as pancreatic cell lineage determination, development, and maintenance [6].

It was reported that single nucleotide polymorphisms (SNPs) in GLIS3 have been related to a variety of pathologies. Increased fasting glucose levels, disturbed β cell function, and an increased risk of T2DM have been related to GLIS3 associated SNPs rs7034200, rs7875253, rs7041847, and rs10814916 [7]. Studies were done with this SNP in T1DM patients [8–10]. Grant et al. [8] found that The A allele was related with an increased risk of T1DM in European population. In 2011, Bradfield and his co-workers found that The A allele was associated with risk for T1DM in Japanese population [9]. On the other hand, Duarte and colleagues found no evidence of individual associations between the rs7020673 and rs10758593 SNPs and T1DM [10].

Given that more research is needed to investigate the association between GLIS3 SNPs and T2DM in diverse populations. Also, no research on this SNP has been conducted in Egypt. We looked into the association of the rs10758593 SNP in the GLIS3 gene with T2DM in Egyptian subjects.

Methods

The participants in this study were split into two groups: 100 T2DM patients recruited from the Endocrinology Clinic, and 100 age and gender matched seemingly healthy people acting as the control group. The International Diabetes Federation (IDF) criteria were used to diagnose T2DM patients in this research.

Sample collection

Ten (10) mL of venous blood were withdrawn by venipuncture from each subject after an overnight fast of 9–10 h and divided as follows: Five (5) mL of venous blood were put into an EDTA vacutainer, inverted several times and inspected to exclude the possibility of clots then stored at -20°C until DNA extraction and detection, two (2) mL of venous blood were placed into another EDTA vacutainer tube for measuring HbA1c. Three (3) mL of venous blood were collected into a yellow-topped serum separator vacutainer tube, allowed to clot at room temperature for 15–30 min prior to centrifugation at 1000g for 10 min for clot separation and serum harvesting, for glucose and insulin assessment.

DNA extraction and qPCR

Using the QIAamp DNA blood mini kit, deoxyribonucleic acid (DNA) was extracted from plasma (QIAGEN, Germany). The concentration of extracted DNA was calculated using a spectrophotometer to measure absorbance at 260 nm. Meanwhile, the absorbance ratio

(OD260/OD280) at 260 and 280 nm was used to assess the quality of extracted DNA. A ratio of about 1.8 was commonly accepted.

For each sample, a PCR reaction was set up. The following reaction volume was set: 2 μL of DNA extract, 10 μL of TaqMan Universal PCR Master Mix, 7 μL of DNase free water, and 1 μL of SNP Genotyping Assay 20 \times working stock comprising sequence-specific forward and reverse primers to amplify the GLIS3 gene promoter area and two TaqMan MGB probes to differentiate between the two alleles. The context sequence for rs10758593 was [VIC/FAM]:

AACCAAAAAGATTTTAAAGAAAAAC[A/G]TAA
ATAAGTTCAGAAAG TACCATGC

The PCR was carried out with the use of an Applied Biosystems Step One Real-Time PCR System. For amplification, this procedure was used: initial heat activation at 95°C for 10 min, DNA denaturation at 95°C for 15 s, then annealing at 65°C for 1 min for 40 cycles.

Statistical analysis

IBM SPSS statistics were used to analyze the data (V. 22.0, IBM Corp., USA, 2013). The median and interquartile range were used to represent nonparametric data, the mean and standard deviation for parametric data, and the percentage for qualitative data. In the case of nonparametric data, the Wilcoxon rank sum test was applied to compare two independent groups. The Chi-square test was used to explore the connection between two variables or to compare two independent groups in terms of categorized data. A p value < 0.05 was considered significant.

Results

Using the Wilcoxon rank sum test, comparison statistics of demographic and routine laboratory tests between T2DM patients and the control group revealed a significant difference in BMI ($p=0.042$) and a highly significant difference in glyated hemoglobin (HbA1c), as well as serum fasting insulin, fasting blood glucose levels, and HOMA-IR (p 0.001, respectively) (Table 1).

The descriptive and comparative statistics of the genotypic frequencies of the GLIS3 rs10758593 (A/G) polymorphism among T2DM patients and control subjects are given in Table 2. In terms of genotypic frequencies, the difference between patients and controls was statistically significant ($p=0.003$). In T2DM patients, 61% had the heterozygous AG genotype, and 39% had the AA genotype. On the contrary, 81% of the controls had AG genotype, 18% had AA genotype, and 1% had GG genotype.

Descriptive and comparative statistics of routine laboratory tests between different genotypes among T2DM

Table 1 Comparative statistics of routine laboratory tests between the patients' group and the control group using Wilcoxon rank sum test

Parameter	Group I T2DM patients (n = 100)	Group II control (n = 100)	z value	p value	Sig.
Age (years) Median (IQR)	52 (46–58)	52 (45.25–58)	– 0.257	0.797	NS
BMI Median (IQR)	29 (27–31)	28.05 (25.7–30.95)	– 2.029	0.042	S
HbA1c (%) Median (IQR)	8.1 (7.2–9.775)	5.3 (4.8–5.4)	– 12.23	<0.001	HS
Fasting blood glucose (mg/dL) Median (IQR)	188.5 (136.5–242.75)	88 (83–92)	– 12.158	<0.001	HS
Fasting insulin (mIU/L) Median (IQR)	15 (12–20)	6 (4–8)	– 11.147	<0.001	HS
HOMA-IR Median (IQR)	7.41 (4.69–10.45)	1.25 (0.91–1.81)	– 12.122	<0.001	HS

IQR interquartile range, p value probability, BMI Body mass index, T2DM type 2 diabetes mellitus, HbA1C glycated hemoglobin, HOMA-IR homeostatic model assessment for insulin resistance, n number, NS non-significant, S Significant, HS highly significant

Table 2 Descriptive and comparative statistics of GLIS3 rs 10,758,593 SNP genotypic frequencies among T2DM patients and control subjects using Chi-square test (χ^2)

Genotypes	Groups		χ^2	p value
	group I (Patients) (n = 100) n (%)	Group II (controls) (n = 100) n (%)		
AA (homozygous mutant type)	39 (39%)	18 (18%)	11.554	0.003
AG (heterozygous type)	61 (61%)	81 (81%)		
GG (homozygous wild type)	0 (0%)	1 (1%)		

n number, p value probability value

Table 3 Descriptive and comparative statistics of routine laboratory tests between different genotypes among T2DM patients using Wilcoxon rank sum test

	Patients (T2DM) (n = 100)		z value	p value	Sig.
	AA (n = 39)	AG (n = 61)			
Age (years) Median (IQR)	53 (46–58)	51 (46–58)	– 0.134	0.893	NS
BMI Median (IQR)	29 (27.1–31)	29 (27–31)	– 0.361	0.718	NS
HbA1C (%) Median (IQR)	9.1 (7.4–10.6)	7.7 (7.0–8.8)	– 2.588	0.01	S
Fasting blood glucose (mg/dL) Median (IQR)	223 (168–298)	175 (130–217)	– 3.032	0.002	S
Fasting insulin(mIU/L) Median (IQR)	18 (16–24)	13 (11–17)	– 4.641	<0.001	HS
HOMA-IR Median (IQR)	10.49 (8.69–13.14)	5.84 (4.16–7.95)	– 5.307	<0.001	HS

IQR interquartile range, p value probability, BMI body mass index, T2DM type 2 diabetes mellitus, HbA1C glycated hemoglobin, HOMA-IR homeostatic model assessment for insulin resistance, n number, NS non-significant, S Significant, HS highly significant

are given in Table 3. HbA1C and fasting blood glucose were significantly higher in the AA genotypic subgroup compared to the AG genotypic subgroup ($p=0.01, 0.002$, respectively). Moreover, fasting insulin and HOMA-IR levels in the AA genotype were substantially higher than in the AG genotype subgroup ($p<0.001$, respectively).

Regarding the renal function, there was no statistical significant difference in creatinine, BUN, and uric acid ($p=0.534, 0.983, 0.980$, respectively) but urinary albumin creatinine ratio was significantly higher in the AA genotypic subgroup compared to the AG genotypic subgroup ($p=0.023$) (Table 4).

The statistical comparison between diabetic patients with retinopathy and diabetic patients without retinopathy regarding each genotype using Chi-square test is shown in (Table 5). Among the diabetic patients with retinopathy, 63.6% had AA homozygous genotype and 36.4% had AG heterozygous genotype. Regarding diabetic patients without retinopathy, 33.3% had AA genotype and 66.7% had AG genotype. There was statistically significant difference between both groups regarding genotypic distribution ($p=0.007$).

The statistical comparison between diabetic patients with retinopathy and diabetic patients without retinopathy regarding each genotype using Chi-square test is

shown in Table 6. Among the diabetic patients with neuropathy, 50% had AA homozygous genotype and 50% had AG heterozygous genotype. Regarding diabetic patients without neuropathy, 37.8% had AA genotype and 62.2% had AG genotype. There no was statistically significant difference between both groups regarding genotypic distribution ($p=0.348$) (Table 6).

Correlation study among diabetic patients between HbA1c level and different studied parameters using ranked Spearman’s correlation coefficient test is given in Table 7. In diabetic patients, HbA1c showed significant correlation with fasting insulin ($p=0.039$) and highly significant correlation with fasting glucose, HOMA-IR, and alb/creat ratio ($p<0.01$ respectively), while there was no correlation between HbA1c and BMI ($p=0.744$).

Discussion

The transcription factor Gli-similar 3 (GLIS3) is essential for the maturation pancreatic cells, as well as the control of insulin gene expression in adults [7].

GLIS3 interacts with transcription factors specific for beta cells to directly and indirectly activate insulin gene transcription in rat insulinoma cells [11]. GLIS3 knock-down enhanced proinflammatory cytokines and palmitate-induced beta-cell death, suggesting that GLIS3

Table 4 Descriptive and comparative statistics of renal functions between different genotypes among diabetic patients using Wilcoxon rank sum test

Genotype	Patients (n = 100)				
	AA	AG	z	p value	Sig
Serum creatinine (mg/dL) Median (IQR)	1 (0.6–1.4)	0.9 (0.65–1.1)	– 0.621	0.534	NS
BUN(mg/dL) Median (IQR)	15 (9–18)	14 (9–17)	– 0.021	0.983	NS
Uric acid (mg/dL) Median (IQR)	4.1 (2.6–5.4)	4 (3–5.3)	– 0.025	0.98	NS
Urinary alb/creat ratio (mg/g) Median (IQR)	29 (27.1–31)	27 (25.3–29.9)	– 2.278	0.023	S

n number, IQR interquartile range, Alb/creat ratio Albumin/creatinine ratio, BUN blood urea nitrogen

Table 5 Statistical comparison between diabetic patients with and without retinopathy regarding each genotype using Chi-square test

Genotypes	Groups			
	Patients with retinopathy (n = 22)	Patients without retinopathy (n = 78)	X ²	p value
	n (%)	n (%)		
AA (homozygous mutant type)	14 (63.6%)	26 (33.3%)	7.389	.007
AG (heterozygous type)	8 (36.4%)	52 (66.7%)		

n number, p value probability value

Table 6 Statistical comparison between diabetic patients with and without neuropathy regarding each genotype using Chi-square test

Genotypes	Groups		χ^2	p value
	Patients with Neurological symptoms (n = 24)	Patients with Neurological symptoms (n = 76)		
	n (%)	n (%)		
AA (homozygous mutant type)	11 (45.8%)	28 (36.8%)	0.882	0.348
AG (heterozygous type)	13 (54.2%)	48 (63.2%)		

n number, p value probability value

Table 7 Statistical correlation between HbA1c and different studied parameters among diabetic patients using ranked Spearman's correlation coefficient test

Parameter	HbA1c in T2DM patients		
	r	p	Sig.
BMI	0.037	0.744	NS
Fasting blood glucose (mg/dL)	0.644	<0.01	HS
Fasting insulin (mIU/L)	0.231	0.039	S
HOMA-IR	0.531	<0.01	HS
Alb/creat ($\mu\text{g}/\text{mg}$)	0.81	<0.01	HS

BMI Body mass index, T2DM type 2 diabetes mellitus, HbA1C glycated hemoglobin, HOMA-IR homeostatic model assessment for insulin resistance, NS non-significant, S Significant, HS highly significant, Alb/creat ratio Albumin/creatinine ratio

expression is necessary for beta-cell survival [12]. Both T2DM and T1DM are thought to be caused by malfunction of these pathways. GLIS3 may also play a role in compensatory insulin resistance (IR)-induced beta-cell proliferation and expansion in mice, which can lead to T2DM if disturbed [13]

An association has been identified between common GLIS3 polymorphisms and T1DM, T2DM, and gestational diabetes mellitus (GDM), in addition to different measures of β -cell function, such as fasting blood glucose or Homeostatic Model Assessment of cell function (HOMA-B) [14]. Although it has been suggested that T1DM and T2DM have a shared genetic loci, only a few susceptibility genes have been related to the two forms of DM, including GLIS3, cordon-bleu WH2 repeat protein (COBL) and insulin (INS) [15].

The current investigation investigated the possible relationship of the GLIS3 rs10758593 (A/G) gene polymorphism with T2DM patients based on previous findings. One hundred (100) T2DM patients from the Endocrinology Clinic and 100 non-diabetic control participants who were age and sex matched and satisfied the exclusion criteria were included in our research. Using real-time PCR, we looked for the

GLIS3 rs10758593 (A/G) polymorphism in our chosen population.

Our results revealed the presence of the mutant genotype (AA) in 39% of the patients' group and in 18% of the control group ($p < 0.05$). The AG (heterozygous) genotype was found in 61% of the patients' group and in 81% of the control group ($p < 0.05$). Unexpectedly, the GG genotype was detected in only 1% of the controls, while it could not be detected in any of our patients' samples. This may be attributed to the genetic variation in different population, and to relatively small sample size included in the study.

Our data showed that the frequencies of the mutant genotypes; AA and AG, significantly varied between patients and controls. This finding goes with the GWAS meta-analysis which demonstrated that rs10758593 A allele was associated with risk for T2DM in European population [16]. According to Boesgaard et al., GLIS3 polymorphism is linked to a reduced glucose-stimulated insulin response, resulting in hyperglycemia and T2DM [17]. Furthermore, GLIS3 polymorphism is linked to T2DM and impaired fasting glucose in the Chinese population, according to LIU and colleagues [17], which is largely mediated by poor beta-cell activity [18].

Several studies were also done with this SNP in T1DM patients [8–10]. Grant et al. [8] found that The A allele was related with an increased risk of T1DM in European population [8]. Bradfield and his co-workers [9] found that The A allele was associated with risk for T1DM in Japanese population. On the other hand, Duarte and colleagues found no evidence of individual associations between the rs7020673 and rs10758593 SNPs and T1DM. They did state, however, that the frequency of haplotypes with more than three minor alleles of these SNPs was higher in T1DM patients compared to controls [10].

Dooley et al. [19] explained previous results by stating that there are numerous chromosomal loci that impact risk of both T1DM and T2DM and identified a

high enrichment of T1DM link among known T2DM risk loci. Another study by Liston et al. [20] argued that T1DM and T2DM are both caused by β cell fragility, which results in significant cell death.

Therefore, given that the SNP identified is located in the intronic regions, the precise mechanisms by which these SNPs may contribute to T2DM pathogenesis are still unknown [21]. After searching the database for potential functional evidence of the analyzed SNP, we discovered evidence of CTCF (transcriptional repressor) and CEBPB (CCAAT/enhancer-binding protein beta) transcription factor binding sites (TFBS) overlapping this SNP's position [22]. Furthermore, Duarte et al. [10] discovered long noncoding RNA (lncRNA) predicted to bind in the positions of the rs7020673 and rs10758593 SNPs [18]. As a result, the rs7020673C and rs1075859A alleles may influence GLIS3 gene expression by altering potential TFBS or lncRNA binding. The expression and regulation of GLIS3 are required for proper cell development and maintenance of postnatal function [7].

In our study, we attempted to investigate the relationship between genotypic distribution and glycemic control. When AA genotype patients were compared to AG genotype patients, there was a statistically significant increase in HbA1C. Furthermore, the AA genotype had a highly significant increase in fasting blood glucose, fasting insulin, and HOMA-IR. These findings were consistent with the findings of Duarte et al. [10], who encountered that HbA1c levels were higher in subjects with the rs10758593 A/A genotype compared to G allele carriers [18]. Similarly, Aylward et al. [22] revealed that GLIS3 rs10758593 risk alleles were linked to higher fasting glucose levels and lower homeostatic model assessment for beta-cell function (HOMA-B). These findings suggest that the presence of the A allele is linked to insulin resistance and poor glycemic control [22].

We attempted to investigate the relationship between genotypic distribution and diabetic complications. Surprisingly, we discovered a statistically significant difference in genotypic distribution between patients with retinopathy and patients without retinopathy. According to Dimitri et al. [23], in mouse models, GLIS3 is expressed in a dynamic pattern during eye development, first in the dorsal optic vesicle and then in the lens and the retina, which supports the presentation of eye diseases in patients with GLIS3 mutations. On the contrary, Duarte et al. [10] in their study could not find statistical significant difference between patients with retinopathy and patients without retinopathy regarding genotypic distribution [17].

Although our results showed no statistically significant difference in kidney function test (creatinine, BUN and uric acid), however, our data revealed a statistical

significant difference in urinary albumin/creatinine ratio ($p < 0.05$). Duarte et al. [10] did not find statistically significant difference between patients with and without nephropathy regarding genotypic distribution [18]. In our study, we did not find statistically significant difference between patients with neuropathy and patients without neuropathy regarding GLIS3 gene polymorphism.

In our study, we found significant correlation between HbA1C and fasting glucose levels. Dave et al. [24] also found that HbA1 C level was increased in diabetics, and it showed correlation with fasting blood glucose. Same results has been reported by various workers as Shrestha et al. [25], Swetha [26], and Rosediani et al. [27]. The more FPG values increase, the more HbA1c values increase. The increase in plasma glucose values contribute to bind glucose-hemoglobin more (glycation reaction) and consequently make higher values of HbA1c [25].

Moreover, we found significant correlation between HbA1C and fasting insulin and HOMA-IR. Similarly, Al-Hakeim et al. [28] found HbA1c increased in T2DM patients and had correlation with levels of fasting insulin, HOMA-IR. Also, Hou et al. [29] found significant correlation between HbA1c, fasting glucose levels, fasting insulin, and insulin resistance. Insulin resistance has a correlation with the decrease in fasting insulin value. As insulin maintains the glucose blood homeostasis by facilitating cellular glucose uptake, the increase in serum glucose will induce β -cells to increase insulin secretion. This will affect the increase in blood glucose value [29].

We found significant correlation between HbA1c and alb/creat ratio. This come in agreement with Haque et al. [30] who stated that serum creatinine and alb/creat ratio had significant positive correlation with HbA1c. Moreover, Chiu et al. [31] also reported that Higher HbA1C variability is more likely to progress to microalbuminuria. Fluctuating or persisting high glucose levels can induce oxidative stress, overproduction of reactive oxygen species, and endothelial dysfunction and contribute to microvascular (nephropathy, retinopathy, and neuropathy) in T2DM patients [30].

Many factors can explain the disparities in the findings and conclusions of diverse studies. Single-locus effects were shown to be insufficient to explain complex chronic illnesses. Thus, when the single polymorphism effect is absent or insufficient, it is critical to characterize the other gene polymorphisms associated with susceptibility, keeping in mind the concept of multilocus genetic interactions.

Furthermore, the duration of diabetes and other characteristics, such as differences in various genetics, environmental factors, ethnic stratification, research design variation, and sample size, vary between studies and impact the outcomes.

Limitations

Our results provide the insight into the contribution of GLIS3 gene polymorphism 10758593(A/G) to T2DM in the Egyptian population. However, we encountered some limitations, such as the relatively small sample size. Therefore, further large, multi-ethnic studies on larger sample size are recommended to clarify the statistical significance of the association of the A allele and the AA genotype of the GLIS3 rs 10758593 with T2DM and to confirm the role of GLIS3 gene polymorphism in disease susceptibility and pathogenesis.

Conclusion

In conclusion, we demonstrated significant association between GLIS3 rs 10758593(A/G) and T2DM in Egyptian population. A significant association between GLIS3 rs 10758593 mutation and the glycemic control was also found. Additionally, a significant association of the GLIS3 rs10758593 mutation and presence of diabetic retinopathy and nephropathy was detected. However, association between the polymorphism and diabetic neuropathy could not be revealed.

Abbreviations

Alb/creat ratio: Albumin/creatinine ratio; BMI: Body mass index; BUN: Blood urea nitrogen; CCND2: Cyclin D2; CEBPB: CCAAT/enhancer-binding protein beta; COBL: Cordon-bleu WH2 repeat protein; DM: Diabetes mellitus; DNA: Deoxyribonucleic acid; FPG: Fasting plasma glucose; GDM: Gestational diabetes mellitus; GLIS3: Gli-similar 3; GWAS: Genome wide association studies; HbA1C: Hemoglobin A1c; HOMA-B: Homeostatic model assessment for beta-cell function; HOMA-IR: Homeostatic model assessment for insulin resistance; IDF: International Diabetes Federation; INS: Insulin; IR: Insulin resistance; Lnc RNA: Long noncoding RNA; MGB: Minor groove binder; Ngn3: Neurogenin 3; PCR: Polymerase chain reaction; RNA: Ribonucleic acid; SNP: Single nucleotide polymorphisms; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; TFBS: Transcription factor binding sites.

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Authors' contributions

MM collected the samples of the patients in addition to their demographic, clinical and laboratory data and wrote the manuscript. MM, AI, MM, AA and NM analyzed and interpreted the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

The data within this paper and other findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The approval of the study was taken from the Institutional Ethics Committee of the Faculty of Medicine, Ain Shams University (Ethical Committee's

reference number: 195/2019; 24/7/2019). Written informed consent was taken from all patients who were invited to participate in the research.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interest to declare.

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