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11β Hydroxysteroid dehydrogenase type 1 Gene Expression in Obesity and its Complications

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Abstract

Background: 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an enzyme greatly expressed in the adipose tissue and acts as a reductase (convert inactive cortisone into active cortisol). Previous study assumed that the pathophysiology of obesity might be elaborated by tissue-specific dysregulation of cortisol metabolism. Numerous studies have assessed 11β-HSD1 gene polymorphisms and obesity risk. However, there is still a lack in the published literature evaluating the association between 11β-HSD1 gene expression and the risk of obesity and its related diseases.

Objective: This study was carried out to investigate the relationship of 11β-HSD1 gene expression with obesity, diabetes, and hypertension in subcutaneous adipose tissue. Moreover, this study correlates 11β-HSD1 gene expression with various parameters in obese patients.

Patients and methods: Our study was conducted on 74 subjects; they were selected from kasr Al Aini Hospital, Surgical Department. Obese patients (n=56) with BMI ≥30 kg/m^2 were divided according to obesity complications into obese (n=26), obese hypertensive (n=14) and obese diabetic (n=16) groups beside 18 age- and sex-matched normal weight healthy subjects as control group. The expression of 11β-HSD1 was evaluated with real-time PCR.

Results: There was a significant difference between obese and controls in HSD11β1 gene expression level and we found a significant difference in obese patients with diabetes and hypertension compared to normal weight healthy controls. Furthermore, the correlation and regression analysis showed that the 11β-HSD1 gene expression was correlated with fasting blood glucose and triglycerides levels in obese patients.

Conclusion: The study shows a significant association between subcutaneous adipose tissue 11β-HSD1 gene expression and obesity. Moreover, the subcutaneous adipose tissue expression level of 11β-HSD1 gene was correlated to fasting plasma glucose level and also correlated to triglycerides. So the 11β-HSD1 gene expression is significantly increased the risk of diabetes mellitus and hypertension in obese individuals.

Keywords: 11β-HSD1, gene expression; obese; diabetes mellitus; hypertension.

1. Introduction

Obesity has become an accumulative public health problem worldwide over the last few decades, and its linked disorders vary by region. For instance obesity is related to diabetes, hypertension, angina and arthritis in China, Russia and South Africa; however it is linked to hypertension in India [1]. More so obesity could lead to a varied range of other diseases [2, 3]. Obesity is generally defined as an extreme accumulation or irregular body fat (BF) distribution, disturbing health [4]. Primarily, obesity is classified via a very limited criterion which is the body mass index (BMI, kg/m^2) [5]. Obesity is related to other diseases as hypertension, cardiovascular diseases, stroke, type 2 diabetes mellitus (T2DM), dyslipidaemia, hepatic steatosis, gallbladder issues, osteoarthritis, sleep apnea, and other breathing difficulties as well as specific types of cancers like

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endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon, all of these disorders could increase the risk of mortality [6]. Some cases correlated to disorders of the pituitary, thyroid, and adrenal glands are considered an independent pathology but may point to obesity [7, 8].

Numerous genes polymorphisms are involved in multifactorial polygenic obesity, environmental factors such as diet, absence of exercise, ultra-processed meals, fast food, microbiome, and chemical pollutants have an impact on this subtype that could change gene expression [9]. 11-hydroxysteroid dehydrogenase type 1 (11β-HSD1), is a microsomal enzyme that is extremely expressed in critical metabolic tissues as well as adipose tissue, the liver, and the central nervous system. Inside these tissues, 11β –HSD1 converts the inactive cortisone to active cortisol, a member of the family of short-chain dehydrogenases that stimulates glucocorticoid receptors [10]. Glucocorticoids play a significant role in controlling the metabolism of proteins, lipids and carbohydrates. Therefore, elevated glucocorticoids levels could be a contributing factor in the development of obesity, hypertension and type 2 diabetes mellitus [11].

The circulating cortisol levels are normal or even reduced in common obesity, but the high exposure of tissue to active glucocorticoids due to increase the activity of 11 β -HSD1 might elucidate the similarity between idiopathic obesity and Cushing's syndrome [12]. Numerous studies in rodents and humans have clarified the involvement of 11 β -HSD1 in the etiology of obesity and the difficulties associated with it. Many characteristics of the metabolic syndrome, including BMI [13, 14], insulin sensitivity, and blood pressure, have been linked positively by a number of findings in humans [15, 16]. Consequently, 11β-HSD1 and its inhibitors are both attractive targets in the pharmacotherapy of obesity, type 2 diabetes mellitus, and hypertension due to the involvement of 11-HSD1 enzyme in the development of these disorders [11].

Furthermore, recently it has been shown that there is a positive correlation between 11 β-HSD1 and obesity in the adipose tissue of obese women [15], which proposed that glucocorticoids could have an essential role in the disturbance of fatty acid recycling detected in idiopathic obesity. In humans short-term studies concerning to weight loss revealed no alterations in 11 β- HSD1 gene expression in the whole AT [17, 18] however a significant rise in mRNA levels of 11β- HSD1 in isolated adipocytes [18]. According to a study by Purnell et al. [19], men's adipose 11β-HSD1 gene expression significantly reduced after six months of established weight loss.

This study was carried out to investigate the relationship of 11β HSD1 gene expression with obesity, T2DM, and hypertension in subcutaneous AT from obese subjects with or without diabetes or hypertension. This study also correlates 11β-HSD1 gene expression with various parameters in obese patients.

2. Subjects and Methods

The study conducted on 56 obese patients with or without type-2 diabetes or hypertenssion (BMI ≥30 kg/m^2) from kasr Al Aini Hospital, Surgical Department (patients scheduled for bariatric surgery for obesity), Body weight (kg) divided by height squared (m^2) was used to calculated the body mass index (BMI). Obese patients were divided into obese, obese with hypertention, obese with diabetes groups (n=26;14;16; respectively) according to obesity complications. We also classified obese patients according to BMI [20] into normal weight: BMI < 30kg/m^2; class I obesity: BMI 30–34.9 kg/m^2; class II obesity: BMI 35–39.9 kg/m^2; class III obesity: BMI ≥ 40 kg/m^2. Beside 18 normal weight healthy individuals matching the age and sex distributions of the obese patients (underwent an elective minor surgical operations i.e hernia) were served as control. Obese patients with hepatic or renal disease, hypo- or hyperthyroidism, acute or chronic infectious or immunological illnesses, growth hormone insufficiency, pregnancy, cancer, and breastfeeding women were all excluded from this study. The National Research Centre's Medical Ethics Committee approved the study protocol, and each participant in this investigation provided written consent. Blood and subcutaneous tissue samples were taken from every participant. All individuals subjected to physical examinations and routine biochemical analyses of their blood samples after an overnight fasting. In the current study, quantitative real-time PCR (qRT-PCR) was carried out to investigate 11- hydroxysteriod dehydrogenase 1 (11β-HSD1) gene expression in subcutaneous adipose tissue from obese subjects.

RNA extraction, reverse transcription and real-time PCR

Following the manufacturer's instructions, RNA was extracted from 1 g of tissue from each participant using a qiazol extraction kit from Qiagen. The extracted RNA concentration was then measured by a nanodrop spectrophotometer, and the quality was assessed using an A260/A280 ratio of 1.8–2.0 and agarose gel electrophoresis. The resulting cDNA was diluted 20 times with double-distilled water for reverse transcription using an archive RT kit (Qiagen,

Hilden, Germany), reactions include 15-µl RNA, 4-µl 5x Buffer containing nucleics mix and 1µl reverse transcriptase. Relative qRT-PCR was carried out as described previously, the thermocycling conditions for RT‑qPCR were as follows: Preheating for 10 min at 95˚C; followed by 40 cycles at 95˚C for 15 sec and 60˚C for 60 sec [21]. Target gene 11ß-HSD1 primers were: F: 5′-AGCGAGGTCAAAAGAAACTCTA-3′ R: 5′-TGAGAATGAGCATGTCTAGTCC-3′ [22] and endogenous control F 5′-GAGTGTAAGGACCCATCGGA-3′ R 5′-CCTCCAATGGATCCTCGTTA-3′, the 18S ribosome sequence (Hs99999901_s1), were both subjected to SYBR green master mix gene expression tests (Applied Biosystems, Foster City, CA). Every reaction was carried out in triplicate, and in every replicate plate both non-template and non-polymerase controls were incorporated. Data were normalized against the lowest coefficient of variation, 18S, and show statistical differences with $2^{-\Delta\Delta}$CT equation.

Statistical analysis

All data were transformed and operated using SPSS (20.0) software program. ANOVA test was used for comparison between the studied groups and data are presented as mean ± SE. A linear regression analysis and Pearson's-test were used to find out various parameters affecting the gene expression levels. P-values < 0.05 were considered significant. Significant expression levels were graphically represented by error bars graphs.

3. Results

3.1. Clinical characteristics of obese patients and normal weight controls

The anthropometric and clinical data of the subjects enrolled in the study are summarized in table (1). There were no substantial differences in age or gender between the obese participants and normal weight controls. The BMI, fasting glucose, insulin, HOMA-IR, total cholesterol (TC), triglycerides (TG) and LDL-cholesterol (LDL-c) were significantly higher in the obese subjects compared with controls (Table 1).

3.2. Validation of 11-Beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) gene expression in individual tissue samples

To validate the possibility of using 11-Beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) gene as a marker for obesity, the expression levels of 11β-HSD1 in tissue of participants were assesed by real-time quantitative PCR (qRT-PCR). The results showed that the 11β-HSD1 expression levels were increased in the obese patients than in normal weight subjects (*P* value = 0.038; Figure 1), the means of gene expression values were 2.52 and 1.88 in obese and normal weight subjects respectively. Indeed the obesity complications, 11β-HSD1 expression levels in obese patients with hypertension and type 2 diabetes (Means±SE=2.9±0.2 and 2.86±0.25; respectively) were more significantly higher compared to controls (*P*=0.01; Table 2 &Figure 2).

To further explore the correlation between 11β-HSD1 expressions and obesity, we stratified the grade of obesity using BMI. In comparison with the normal weight controls, class I (n=11), class II (n=19) and class III (n=26) obese patients had significantly higher levels of 11β-HSD1 gene expression in obese, obese hypertensive and obese diabetic with *P* value = 0.02; 0.043; 0.005; respectively (Fig. 3). The expression levels of 11β-HSD1 gene revealed a tendency to gradual elevated significantly with class I & II of obesity, although this expression was increased in class III obese patients but not a gradually significant (Figure 3).

3.3. Correlation of tissue 11β-HSD1 gene expression levels with obesity

The expression levels of 11β-HSD1 gene were positively significantly correlated with fasting blood glucose (*r* = 0.296* and *P* value = 0.027; Table 3) so, the higher the fasting glucose, the higher the 11β-HSD1 gene expression levels in obese patients.

3.4. Linear regression analysis of 11β-HSD1 gene expression and lipid profile in obese patients

Linear regression was established in order to examine the linear relationship between the expression of 11β-HSD1 gene and lipid profile in the obese subjects. In table 4, 11β-HSD1 gene expression levels and triglycerides regression analysis showed a linear positive association between 11β-HSD1 expression and triglycerides, in which the triglycerides was the independent variable and 11β-HSD1 was the dependent variable so, the greater the triglycerides, the greater the 11β-HSD1 expressions in obese patients at significant level = 0.012.

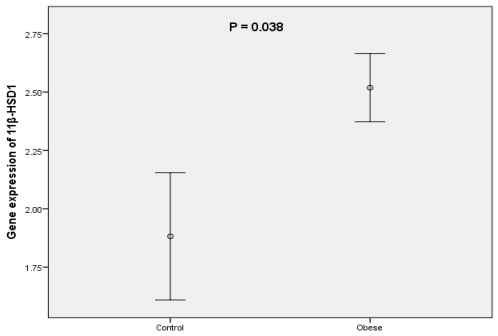


Figure 1: The gene expression of 11-Beta-hydroxysteroid dehydrogenase type 1 in obese and control groups

Mean values of indicated 11β-HSD1gene expression and error bars indicating SEM are shown with *p* value = 0.038.
Control group: Healthy subjects with normal weight BMI 20-29.9 kg/m^2.
Obese group: Total obese patients BMI ≥ 30 kg/m^2.

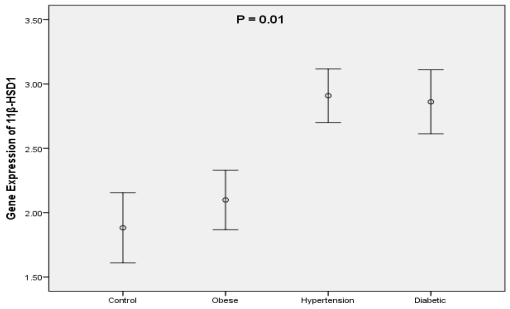
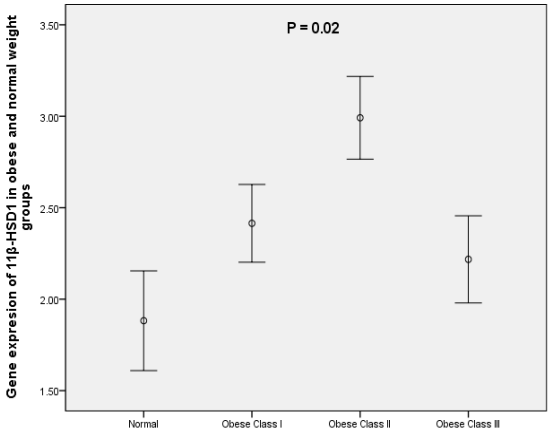
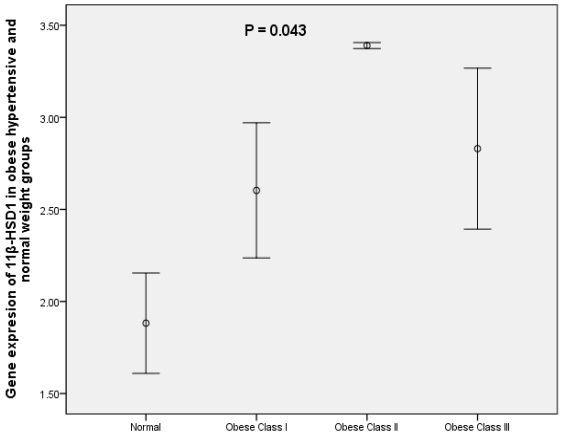


Figure 2: The gene expression of 11β-HSD1 in obese, hypertension, diabetic and control groups

Mean values of indicated 11β-HSD1gene expression and error bars indicating SEM are shown with p value = 0.01.
Control group: Healthy subjects with normal weight.
Obese group: Obese patients without complications (Without hypertension or type two diabetes mellitus).
Hypertension group: Obese patients with hypertension as obesity complication.
Diabetic group: Obese patients with type two diabetes mellitus as obesity complication.





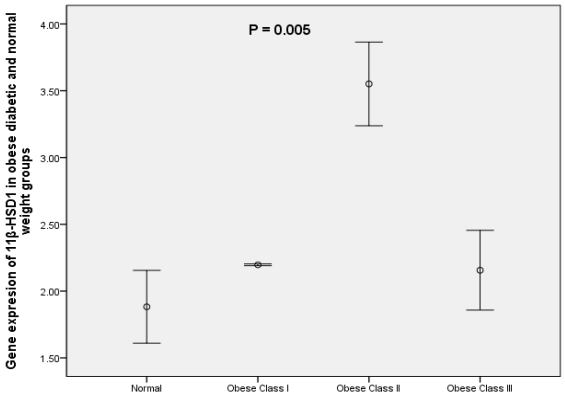


Figure 3: The gene expression of 11-Beta- HSD1 according to obesity classes in obese, obese hypertensive, obese diabetic and normal weight controls

Mean values of indicated 11β-HSD1gene expression and error bars indicating SEM.
Normal weight: BMI < 30kg/m^2
Class I obesity: BMI 30–34.9 kg/m^2
Class II obesity: BMI 35–39.9 kg/m^2
Class III obesity: BMI ≥ 40 kg/m^2

Table 1

Clinical characteristics of obese patients and normal weight controls

Variables	Obese (n=26)	Obese with hypertension (n=14)	Obese with diabetes (n=16)	Control (n = 18)	*P* value
Age	37.04±1.4	39.07±1.86	38.56±1.39	33.44±1.47	0.07
Sex (male/female)	6/20	5/9	3/13	7/11	0.4
BMI (kg/m^2)	42.5±1.4	40.7±2.7	39±1.3	21.93±0.61	**< 0.001**
Insulin (µlU/ml)	5.95±0.64	4.66±0.7	8.87±0.5	3.29±0.17	**< 0.001**
FG (mg/dL)	94.85±0.7	96.43±2.3	124.56±2.4	88.67±1.58	**< 0.001**
HOMA-IR index	1.26±0.13	1.02±0.16	2.48±0.16	0.73±0.04	**< 0.001**
TC (mg/dL)	170±8.8	178.6±7.3	224.5±4.3	147±2.39	**< 0.001**
TG (mg/dL)	136.6±9	170.4±8	172.4±4	94.28±2.54	**< 0.001**
HDL-c (mg/dL)	57±1.4	55±1.2	57±0.9	53.39±0.86	0.14
LDL- c (mg/dL)	85.9±8.7	89.3±7.6	132.95±4.4	74.75±2.03	**<0.001**

Numeric variables are presented as mean ± SE or numbers.
P value for comparison between obese and control groups.
P value <0.05 are represented in bold font and considered as statistically significant.
BMI: Body mass index FG: Fasting glucose HOMA-IR: homoeostasis model assessment-insulin resistance TC: Total cholesterol TG: Triglycerides HDL-c: High density lipoprotein-cholesterol
LDL-c: Low density lipoprotein-cholesterol

Table 2
The gene expression of 11-Beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in obese and control groups

Gene	Obese (n=26)		Obese with hypertension (n=14)		Obese with diabetes (n=16)		Controls (n=18)		*P* value
	Mean ± SE	**95% CI**	**Mean ± SE**	**95% CI**	**Mean ± SE**	**95% CI**	**Mean ± SE**	**95% CI**	
11β-HSD1	2.1 ±0.2	1.6 – 2.6	2.9±0.2	2.4 – 3.3	2.86±0.25	2.3 – 3.4	1.8±0.3	1.3-2.4	**0.01**

Numeric variables are presented as mean ± SE and 95% Confidence Interval (95% CI).
P value for comparison between obese and control groups.
P value <0.05 are represented in bold font and considered as statistically significant.

Table 3
Pearson's correlation of 11-Beta-hydroxysteroid dehydrogenase type 1 gene with insulin, fasting glucose and HOMA-IR index

Co-variables	Pearson's correlation	
	r	***P* value**
Insulin (µlU/ml)	0.074	0.588
Fasting Glucose (mg/dL)	**0.296***	**0.027**
HOMA-IR index	0.12	0.378

P value <0.05 are represented in bold font and considered as statistically significant
HOMA-IR: homoeostasis model assessment-insulin resistance

Table 4

Linear regression analysis of 11-Beta-hydroxysteroid dehydrogenase type 1 gene and lipid profile in obese patients

Variables	Unstandardized Coefficients		Standardized Coefficients	t	Significant	95% Confidence Interval for B	
	B	Standard Error	Beta			Lower Bound	Upper Bound
TG	0.009	0.004	0.340	2.607	**0.012**	0.002	0.016
HDL	0.035	0.024	0.194	1.484	0.144	-0.012	0.083
LDL	0.000	0.004	-0.012	-.094	0.926	-0.007	0.007

Dependent variable: 11β-HSD1
P value <0.05 are represented in bold font and considered as statistically significant
TG: Triglycerides HDL: High density lipoprotein LDL: Low density lipoprotein

4. Discussion

The HSD11β1 gene encodes the bidirectional enzyme hydroxysteroid (11-beta) dehydrogenase type 1 (11β-HSD1), which is extremely expressed in adipose tissue (AT) [18]. In human studies, overexpression of 11-βHSD1 is associated with obesity, metabolic syndrome, diabetes and hypertension. However, this established association is still unclear [23, 24]. In this concern, multiple genomic studies containing greater and additional homogeneous populations are necessary to recognize exact genetic biomarkers in these disorders [25]. The purpose of this study is to present genetic marker associated to the pathogenesis of obesity and some related diseases in Egyptian patients.

This study showed that there was a statistically significant difference between 11β-HSD1 gene expression level in subcutaneous adipose tissues (SAT) of obese patients and normal weight healthy controls in Egyptian patients. In accordance with our results, a systematic review was conducted in other populations to assess the potential relationship of 11-βHSD1 gene expression in adipose tissue with obesity [23]. Conversely, some research did not support a link between HSD11β1 expression in SAT and central or generalized obesity [26, 27]. From our study and the previous findings, 11β-HSD1 might support preadipocyte differentiation and might be elaborated in the progress of obesity. This could be explained as adipose cells in early differentiation stage displayed a switch from dehydrogenase activity (which inactivates cortisol to cortisone) to reductase activity (which produces active cortisol from inactive cortisone), certifying autocrine generation of cortisol, that induced adipocyte differentiation [28]. Therefore, the fact that 11βHSD1 appeared to be crucial for adipocyte development and for controlling adipose tissue depots suggested that inhibiting 11β-HSD1 could be a successful therapy in obesity [29].

Additionally in this study, 11β-HSD1 expression levels reported highly significant increase in obese patients with hypertension and diabetes, as obesity complications, compared to healthy controls. These results of the current study were consistent with another study by Shukla et al. [30], who found that 11βHSD1 activity is increased in type 2 diabetes mellitus (T2DM). Similarly, genetic association studies were done in in Pima Indians and South Indian populations to study the association of HSD11β1 gene polymorphisms with T2DM and the results showed that HSD11β1 gene was associated with T2DM [31, 32]. Furthermore, Szweda-Gandor et al. provided a basic research on the role of the HSD11B1 gene in the pathogenesis of insulin resistance [33]. Concerning the relation of 11β-HSD1 with hypertension, Bailey [34] study was in agreement with our results who found that 11βHSD1 contributes to hypertension. On the contrary, the association between HSD11β1 polymorphisms and T2DM and metabolic phenotypes were studied in Korean and no substantial link was found [35, 23]. Moreover, the association of HSD11β1 gene variants with diabetes, hypertension, and obesity was examined in a longitudinal population study of American Indians, the results showed that the associations between HSD11β1 gene with diabetes were not statistically significant [36].

Our study suggested that 11β-HSD1 is probable to play a multiple role in adiposity determination and its complications as diabetes and hypertension that

might be owing to tissue-specific regulation of this enzyme. This finding proposed that both adiposity-dependent and independent mechanisms underlie 11β-HSD1 activity's effects on early insulin secretion, insulin resistance, and ultimately improved risk of diabetes in humans [37]. Indeed, raised 11βHSD activity could cause metabolic syndrome development; the metabolic syndrome defined a concurrence of interrelated abnormalities, including dyslipidaemia, visceral obesity, hypertension, and insulin resistance [38]. An 11β-HSD1 inhibitor has been proposed to reverse metabolic syndrome in mice over expressing 11βHSD1 since 11 β HSD knockout transgenic animals show greater insulin sensitivity and are moreover resistant to progress metabolic syndrome when put on a raised fat diet [39]. This has led to the suggestion that elevated 11β HSD1 activity contributes to the progress of T2DM and the metabolic syndrome. Though, future studies in the Egyptian population, other than replication of our results in other metabolically characterized populations are essential to support this suggestion.

The putative important function of 11β-HSD1 in the pathogenesis of visceral obesity and metabolic syndrome has been highlighted in previous human and animal research. As a result of its direct and indirect effects on the kidney and vascular system, 11β-HSD1 increases the glucocorticoid's effect in cells and leads to hypertension [34], more so mice that over expressed 11βHSD1 have severe hypertension as result of elevated angiotensinogen production by the liver [40]. Increased the levels of 11β-HSD1 activity in AT were positively correlated with blood pressure, insulin sensitivity, and markers of central fat storage [41]. The idea that lower glucocorticoid activity in AT may have positive impacts on body composition and the metabolic profile is supported by the concept that gene modification research in rodents and associational studies in humans have emphasized the role of 11β-HSD1 on energy metabolism pathways. Due to the fact that pharmacological inhibition of 11β-HSD1 enhanced lipid profiles, insulin sensitivity, and glucose tolerance in rodents, it has been suggested as an attractive goal [42].

In this study, we stratified the degree of obesity by BMI in order to further investigate the association between 11β-HSD1 expressions and obesity. Compared to the controls with normal weight, class I, class II and class III obese patients had significantly higher levels of 11β-HSD1 gene expression. The expression levels of 11β-HSD1 gene had shown a tendency to elevate gradually with class I & II of obesity, although this expression was improved in class III obese patients but not a gradually significant. In the same line with our study prior studies reported a linear relationship between subcutaneous 11β-HSD1 and BMI [43, 14, 44]. However in Simonyte et al. [45] investigation, this was detected only after weight loss, when the physiological status had altered from morbid obesity to overweight. This may imply that the link between 11β -HSD1 and BMI disappears above a certain BMI threshold and there are variables other than weight gain may affect disturbances in glucocorticoid metabolism, these disturbances in glucocorticoid metabolism may therefore be seen as more of a response to obesity than a cause.

Additionally in the current study, 11β-HSD1 gene expression levels and triglycerides regression analysis showed a linear positive association between 11β-HSD1 expression and triglycerides. Consistent with the finding of the present study, free fatty acid (FA) and triglyceride levels in serum were elevated when 11β-HSD1 was overexpressed in fat; in contrast, 11β-HSD1 knockout mice that were fed ad libitum had much reduced plasma triglyceride levels [46, 47]. Regarding to the correlation between 11β-HSD1 gene expression and fasting blood glucose levels, the expression level of 11β-HSD1 gene was positively correlated with fasting blood glucose this observation was in consistent with Baudrand et al. [48] who found that HSD11B1 expression increased respectively with increasing fasting plasma glucose in morbid obese subjects.

5. Conclusions

The present study demonstrated a significant association between 11β-HSD1 gene expression and obesity. Elevation of 11β-HSD1 gene expression in subcutaneous adipose tissue appears to improve its involvement in severe obesity. Additionally, the expression level of 11β-HSD1 gene was correlated to fasting plasma glucose level and also correlated to triglycerides. So the11β-HSD1 gene expression level was significantly increase the risk for diabetes mellitus and hypertension in obese individuals. These findings reinforce the importance of 11β-HSD1 as a mediator and can be used as therapeutic target in obesity and its related diseases.

6. The limitation of the study:

In order to find the genetic biomarkers that underlie the relationship between obesity and its complications, more research with larger and more homogeneous populations is required. To eliminate false-positive relationships and to decrease systemic biases and technical errors, the findings from these researches should be replicated in several populations with appropriate sample size.

7. Abbreviations: 11-βHSD1: Hydroxysteroid (11-beta) dehydrogenase type 1; IR: Insulin resistance; T2DM: Type 2 diabetes mellitus; BMI: Body mass index; SAT: subcutaneous adipose tissue; AT: adipose tissue; PEPCK: phosphoenol pyruvate carboxykinase C; FA: fatty acid.

8. Competing interests: The authors declare that they have no competing interests.

9. Author contributions: Contributed equally to the work and have approved the final version submitted for publication.

10. Ethical approval: The study was approved by the ethical committee of the National Research Centre, Egypt (Registration number 19-162).

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