Egypt. J. Chem. **Vol. 68,** SI: Z. M. Nofal, pp. 29 - 35 (2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Expression of FASN and PEPCK genes in adipose tissues of obese subjects with and without diabetes mellitus

Mona E. Badr[1], Heba K. Abdelhakim[1], Mohamed A. El-Desouky[1], Mie Afify[2], Waleed I. Hamimy[3], Mohamed D.E. Abdelmaksoud[2], Weaam Gouda[2]*

[1]*Lab of Biochemistry, Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt.*
[2]*Biochemistry Department, Biotechnology Research Institute, National Research Centre, Giza, Egypt.*
[3]*Anesthesia Department, Obesity Surgery Unit, Faculty of Medicine, Cairo University, Giza, Egypt.*

Abstract

Background: The investigation of phosphoenolpyruvate carboxykinase (PEPCK) and fatty acid synthase (FASN) genes that regulate the energy metabolism could enhance the development of preventive intervention strategies for obesity. Therefore, the purpose of this study is to determine the expression of FASN and PEPCK genes and to investigate their potential role in obese patients with or without type 2 diabetes mellitus (T2DM). Moreover, to explore the correlations between the clinical variables and the above -mentioned genes.

Subjects and methods: Forty obese subjects (25 obese non-diabetic and 15 obese diabetic) underwent bariatric surgery; abdominal subcutaneous adipose tissue (SAT) biopsies were collected from them during the surgery, and 15 non-obese subjects served as controls. The expressions of FASN and PEPCK mRNA were evaluated with quantitative real-time PCR technique, and data were analyzed using SPSS software.

Results: There was a statistically significant increase for PEPCK and FASN mRNA in subcutaneous adipose tissue of obese subjects with and without T2DM compared to controls (p-values < 0.001). Additionally, there was an association between FASN expressions and lipid parameters (TC: r=-0.564*, p=0.029; TG: r=0.684**, p=0.005; LDL: r=-0.637*, p=0.011; HDL: r=0.549*, p=0.034) as well as insulin (r=0.581*, p=0.023) and HOMA-IR (r=0.549*, p=0.34) in obese diabetic patients.

Conclusions: The FASN and PEPCK genes are more expressed in subcutaneous adipose tissues of obese individuals than normal controls, regardless of diabetes status. However, more future studies are needed with a larger sample size to assess our findings.

Keywords: obesity, body mass index (BMI), type 2 diabetes mellitus (T2DM), subcutaneous adipose tissue (SAT), phosphoenolpyruvate carboxykinase (PEPCK), fatty acid synthase (FASN).

1. Introduction

Obesity poses a serious threat to public health and is a major contributor to the global burden of non-communicable diseases, including cardiovascular disease, hypertension, type 2 diabetes mellitus (T2DM), and several types of cancer (1). Over the previous four decades, the prevalence rates of obesity have tripled, and by 2045, it is predicted that 700 million people over the world would be affected (2). Likewise, diabetes will become a more serious threat to health over the next few decades (3). Obesity has been linked to the development of diabetes, which is a metabolic disorder (4). Thus, the introduction of new diagnostic biomarkers is crucial for its effective therapy (5). Significant improvements have been made in the management of diabetes mellitus, with encouraging results using a variety of treatment modalities involving gene, stem cell, and medical nutrition therapies, nanotechnology, and alteration in lifestyle (6). Adipose tissue is a crucial metabolic and endocrine organ that serves as an energy reservoir, controls lipid mobilization (7), and plays crucial role in glucose homeostasis (8). Increased adipocyte size may be the cause of adipocyte malfunction, which can then have metabolic spillover effects that unintentionally cause insulin resistance and development of diabetes (5). Also, the prevalence of diabetes has considerably grown in chronically obese people, and has become four times greater than in the general population (9). Meanwhile eighty percent of individuals with T2DM are obese, insulin resistance is linked to both obesity and type 2 diabetes (10). The primary enzyme that controls glycogenolysis and gluconeogenesis is phosphoenolpyruvate carboxykinase (PEPCK). Elevated PEPCK gene expression in diabetic hepatic adipose tissues was connected to elevated glycogenolysis (11). Since insulin controls PEPCK activity, PEPCK gene transcription was reduced when insulin levels were high (12). PEPCK over expression in mice increases adipocyte size, fat mass, and body weight. Accordingly, the PEPCK gene has been linked to obesity and could be a marker for the metabolic rate (13,14).An important lipogenic enzyme is called fatty acid synthase (FASN) may have a major impact on the variability of the weight of abdominal adipose tissue (15). Specifically, FASN is a multifunctional enzymatic complex that is crucial for controlling body weight and preventing the onset of obesity (15–17). FASN may contribute to the microvascular dysfunction associated with diabetes mellitus

*Corresponding author e-mail: weaamgoudaali@mail.com.; (**Weaam Gouda**).
Received date 30 April 2025; Revised date 03 June 2025; Accepted date 02 July 2025
DOI: 10.21608/EJCHEM.2025.380430.11673

(18). Consequently, FASN has been increasingly implicated in the pathogenesis of diabetes and insulin resistance, but the precise mechanisms underlying its role remain undefined (19), and it is unclear whether FASN over expression during insulin-resistant DM affects de novo lipogenesis (19). Furthermore, in obese diabetic mice, increased FASN expression is associated with hepatic metabolic disorders, including hyperinsulinemia, dyslipidemia, and impaired insulin sensitivity (20,21). The role of FASN and PEPCK genes in human diabetes associated with obesity remains to be deciphered; further studies in different populations are needed to evaluate the interaction of these gene expressions with obesity related to T2DM, which may have implications for the management of obesity associated with diabetes mellitus. Hence, in the present study, we aimed to measure the expressions of PEPCK-C and FASN genes in subcutaneous adipose tissues of obese Egyptian patients with or without diabetes mellitus. Additionally, the current study assessed the relationship of the mentioned genes with different clinical parameters linked to obesity and diabetes.

2. Subjects and Methods

Subjects

Abdominal subcutaneous adipose tissue (SAT) biopsies were collected from forty obese subjects with body mass index (BMI) ≥ 30 kg/m^2 who underwent bariatric surgery in surgery Unit-Kasr Al Aini Hospital, Cairo, Egypt. Beside 15 subjects none-obese (BMI < 25 kg/m^2) and non-diabetic (fasting plasma glucose < 100 mg/dL) who underwent elective surgeries matched for age and sex were enrolled as controls. The diagnosis of obesity was according to the National Institutes of Health (22) and the diagnosis of type 2 diabetes was based on the guidelines of the American Diabetes Association (23). The exclusion criteria of the study were steroid treatment, kidney or liver diseases, cancer, pregnancy, and a body weight more than 160 kg to avoid super-super obesity and its comorbidities. Participants were assigned into 3 groups as group 1: Included 15 non-obese and non-diabetic control subjects; group 2: Included 25 obese non-diabetic subjects; group 3: Included 15 obese diabetic.

Specimen collection and preparation

Approximately 1 g of subcutaneous adipose tissue was collected at the site of the transverse abdominal incision throughout the surgery following an overnight fast. The tissue was separated into smaller pieces, snap frozen in liquid nitrogen, and kept at −70°C till genes investigations. Peripheral venous blood samples were collected, allowed to clot and centrifuged. The serum samples were stored at −20°C until used for clinical measurements. Peripheral venous blood samples were collected in sodium fluoride tubes for fasting blood glucose determination.

Blood sample collection and storage

All participants had venous blood samples drawn, which were separated into 2 sections. After being incubated for 15 minutes at 37˚C, the first portion was put into a centrifuge tube and rotated at 3,000 rpm for 10 minutes. Following separation, the sera were kept at -80˚C until the ELISA method was applied to estimate the serum levels of TNF-α and IL-6. The remaining portion was placed in an EDTA-coated tube for whole blood DNA extraction and kept at -80˚C until the TNF-α (rs1800629) was analyzed using real-time polymerase chain reaction (RT-PCR).

Clinical investigations

All patients and controls were subjected to the following investigations using standard laboratory assays to analyze: fasting glucose, lipid profile, liver functions (alanine aminotransferase ALT & aspartate aminotransferase AST), and kidney functions (urea & creatinine), using commercial kits following the manufacturer's instructions through spectrophotometer (Applied Biosystems, USA). Low-density lipoprotein (LDL) was calculated according to the Friedewald's equation (24). Serum human insulin levels were determined by enzyme-linked immunosorbent assay (ELISA) (SunLong Biotech Co., LTD., China; catalogue number: SL0933Hu). The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using HOMA equation (25).

Ribonucleic acid (RNA) isolation and TaqMan real-time reverse transcription-polymerase chain reaction (RT-PCR) of fatty acid synthase (FASN) and phosphoenolpyruvate carboxykinase (PEPCK) genes

Subcutaneous adipose tissue (100 mg) was treated with 1 ml of TRIzol reagent (Invitrogen, Carlsbad, CA, USA) to extract the total RNA. Using TOPscript™ cDNA Synthesis Kit (Daejeon, Korea), the total purified RNA (1 µg) was reverse transcribed into cDNA. The RT-qPCR was carried out in duplicate for each sample using SYBR supermix (Takara, Dalian, China) according to the manufacturer's protocols. A total reaction mixture of volume 20 µL, included 10 µL of SYBR Green master mix, 2 µL of each primer set for each gene, and 2 µL of cDNA (100 ng/µL).

Using nuclease-free water, the final reaction volume was completed up to 20 µL. RT-qPCR reactions were done via PCR system 2700 real-time polymerase chain reaction machine (Applied Biosystems, USA). The PCR amplification: 95 °C for ten minutes, followed by 40 cycles of 94 °C for 15 seconds, 55 °C for 30 seconds, and 70 °C for 30 seconds, then four °C permanently. The primers used for genes detection were shown in table 1. The housekeeping gene beta-actin (β-actin) was used to normalize each gene's expression. The fold difference in gene expression compared to the endogenous control was calculated using the $2^{-\Delta\Delta Ct}$ formula (26).

Table 1: The primers for FASN, PEPCK, and β-actin

	Primers sequences	References
FASN	Forward: 5′-CGCGTGGCCGGCTACTCCTAC-3′ Reverse: 5′- CGGCTGCCACACGCTCCTCT-3′	(27)
PEPCK	F: 5′-AGAGCATAAGGGCAAGGT-3′ R: 5′-GGGAGTTCTCACCAAATC-3′	(28)
β-actin	F: 5′-CCACACCCGCCACCAGTTCG-3′ R: 5′-CTAGGGCGGCCCACGAGGA-3′	(28)

Statistical analysis

The statistical analysis and visualization were implemented using SPSS 22.0 (IBM, USA). The calculation of the statistical power and the sample size was done using PASS 11. The Kolmogorov-Smirnov test was used to determine whether the data was normal. The quantitative data were shown as medians and interquartile ranges for skewed data or mean ± standard deviation (SD) for regularly distributed data. Consequently, One-way ANOVA and Mann-Whitney U test were used as applicable to analyze differences in subject characteristics and gene expressions between the studied groups, respectively. Qualitative data were displayed as numbers (%) using Chi-square (χ^2) test. Additionally, The Spearman correlation analysis was employed to estimate the correlation coefficient (*r*) between gene expression levels and variables. Error bar graphs represented mean and 95% confidence interval for gene expression levels among the studied groups. The *P*-value is considered significant if it was less than 0.05.

3. Results

Clinical variables and characteristics of the studied groups were summarized in table 2. Obese groups (non-diabetic and diabetic) were significantly higher compared with control group regarding to BMI, fasting glucose, insulin, HOMA-IR, and lipid profile.

The mRNA expression levels of the studied genes (FASN & PEPCK) were significantly increased in obese subjects with or without T2DM (Group 2&3) comparing to normal-weight individuals. The comparison between groups 2 and 3 revealed that these genes expressions in group3 were more expressed than group2 but statistically insignificant (Table 3 and Figure 1).

Associations of FASN and PEPCK genes expressions with clinical measurements are shown in tables 4 and 5, respectively. Significant negative correlations were shown between the expression of FASN gene and insulin and HOMA-IR among the obese non-diabetic group. Regarding obese diabetic group, there were significant associations with HOMA-IR, insulin, and lipid parameters.

Table 2: Characteristics and clinical data of studied groups

Variables		Group 1 (n=15) Control	Group 2 (n=25) Obese non-diabetic	Group 3 (n=15) Obese-diabetic	*P* value	*P* value*
Age (year)		37.2±4.5	40.67±7.6	42.53±6.8	0.095	0.402
Gender n(%)	**Male**	6 (40%)	5 (20%)	4 (26.7%)	0.388	0.625
	Female	9 (60%)	20 (80%)	11 (73.3%)		
Body mass index (kg/m^2)		21.88± 2.187	43.39± 7.43	38.23± 5.108	0.000	0.009
Fasting glucose(mg/dL)		89.93±7.87	87.84±8.37	113±12.82	0.000	0.000
Insulin (µIU/mL)		3.48±0.677	6.1±3.26	9.4±1.72	0.000	0.000
HOMA-IR		0.771± 0.157	1.302± 0.652	2.623± 0.580	0.000	0.000
Cholesterol (mg/dL)		150.7±10.1	166.1± 41.53	227± 19.82	0.000	0.000
Triglycerides (mg/dL)		95.53±6.599	138.7± 47.58	171.9± 18.96	0.000	0.004
High density lipoprotein (mg/dL)		52.73± 4.114	57.32± 6.694	56.53±2.722	0.029	0.646
Low density lipoprotein (mg/dL)		78.83±12.88	81.01± 39.1	136.1± 20.41	0.000	0.000
Creatinine (mg/dL)		0.894± 0.1102	0.88± 0.075	0.86± 0.0736	0.584	0.444
Urea (mg/dL)		21.4± 3.542	19.16± 2.656	19.33± 2.968	0.065	0.86
Alanine aminotransferase (IU/L)		21.73± 3.807	19.8± 3.028	20.53± 2.295	0.170	0.471
Aspartate aminotransferase (IU/L)		21.4±3.562	20.24± 1.234	21.47± 2.532	0.199	0.126

One-way ANOVA for quantitative variables and are presented as mean ± SD
Chi-square (χ^2) test for qualitative variables and are represented as numbers (%)
P value: comparing the studied groups; *P** value: comparing obese diabetic and obese non-diabetic groups
P and *P** <0.05 are statistically significant
HOMA-IR: homoeostasis model assessment insulin resistance

Table 3: Fatty acid synthase (FASN) and phosphoenolpyruvate carboxykinase (PEPCK) genes expression among studied groups

Variables	Controls		Obese non-diabetic		Obese diabetic		*P* value	*P* value*
	Median	IQR	Median	IQR	Median	IQR		
FASN gene	1.24	0.94 –1.68	4.99	3.41–7.1	7.02	3.46–8.6	0.000	0.280
PEPCK gene	1.98	1.89 –2.23	19.4	16.2–22.5	19.7	16.9–24.9	0.000	0.472

Mann–Whitney test
Data presented as median and interquartile range (IQR)
P value relative to control group (non-obese and non-diabetic)
*P** value obese diabetic group relative to obese non-diabetic group
P and *P** values are considered significant if < 0.05.

Table 4: Spearman correlations analysis between the levels of the fatty acid synthase gene in subcutaneous adipose tissue and clinical variables

Variables	Control		Total obese		Obese non-diabetic		Obese diabetic	
	rp		*rp*		*rp*		*rp*	
Body mass index (kg/m^2)	-0.084	0.766	-0.033	0.839	0.048	0.818	0.204	0.466
Glucose(mg/dL)	-.0242	0.384	0.135	0.406	-0.017	0.937	0.156	0.579
Insulin (µIU/mL)	0.188	0.501	-0.025	0.880	**-0.445***	**0.026**	**0.581***	**0.023**
HOMA-IR	0.064	0.820	0.020	0.903	**-0.452***	**0.023**	**0.549***	**0.034**
Total cholesterol (mg/dL)	0.114	0.686	-0.069	0.672	-0.012	0.955	**-0.564***	**0.029**
Triglyceride (mg/dL)	0.299	0.280	0.091	0.576	-0.044	0.835	**0.684****	**0.005**
Low density lipoprotein-c (mg/dL)	0.03	0.914	-0.045	0.783	0.034	0.871	**-0.637***	**0.011**
High density lipoprotein-c (mg/dL)	0.023	0.936	0.055	0.738	-0.040	0.850	**0.549***	**0.034**

Control: non-obese and non-diabetic individuals; *r*: correlation coefficient; *p*: *p*-value. The bold format represents the significant *p* values, *p* value is considered significant if < 0.05.

Table 5: Spearman correlations between phosphoenolpyruvate carboxykinase gene levels in subcutaneous adipose tissue and clinical variables

Variables	Control		Total obese		Obese non-diabetic		Obese diabetic	
	rp		*rp*		*rp*		*rp*	
BMI (kg/m^2)	0.408	0.131	-0.075	0.647	-0.22	0.29	0.255	0.359
FG(mg/dL)	-0.49	0.064	0.081	0.618	0.073	0.73	-0.117	0.679
Insulin (µIU/mL)	-0.345	0.208	-0.028	0.863	-0.049	0.814	-0.222	0.426
HOMA-IR	-0.496	0.060	0.025	0.878	-0.022	0.916	-0.202	0.47
TC (mg/dL)	-0.17	0.546	0.095	0.559	0.04	0.851	-0.122	0.665
TG (mg/dL)	-0.179	0.523	0.153	0.347	0.266	0.199	-0.081	0.774
LDL-c (mg/dL)	-0.152	0.589	0.073	0.654	-0.085	0.686	-0.025	0.929
HDL-c (mg/dL)	0.047	0.868	-0.214	0.184	-0.131	0.531	-0.193	0.49

Control: non-obese and non-diabetic; BMI: body mass index; FG: fasting glucose; HOMA-IR: homeostasis model assessment of insulin resistance; TC: total cholesterol; TG: triglyceride; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; *r*: correlation coefficient; *p*: *p*-value is considered significant if < 0.05.

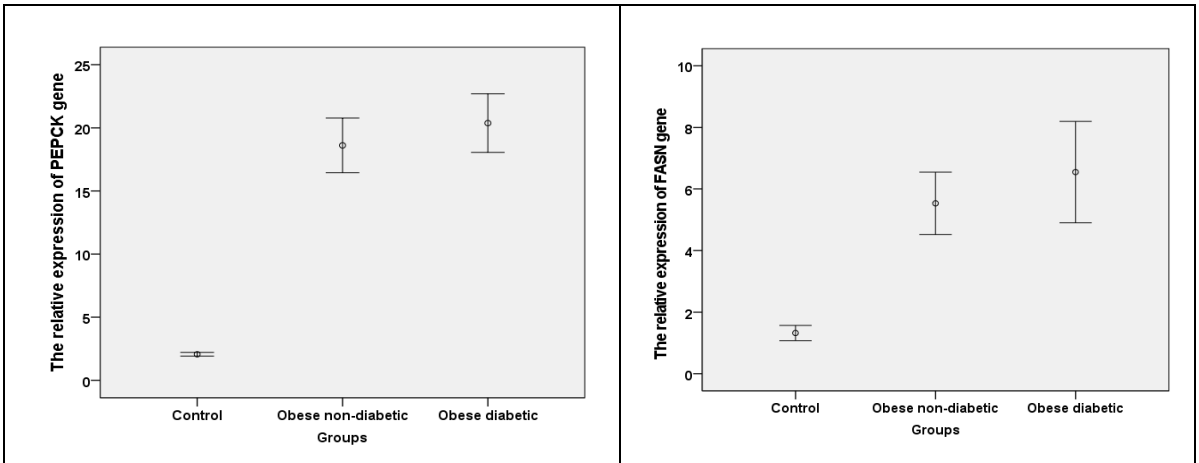

Figure 1: The relative expressions of phosphoenolpyruvate carboxykinase (PEPCK) and fatty acid synthase (FASN) genes in studied groups
Data are represented as error bar for mean and 95% confidence interval

4. Discussion

Obesity is one of the most common metabolic diseases and poses a significant worldwide public health concern (29–32). The prevalence of obesity has increased at an alarming rate (33), which could result in an increase in the number of patients affected by its complications, including the most devastating T2DM (34–36). Prior study showed a significant association between subcutaneous adipose tissue (SAT) gene expression and obesity. Moreover, its expression level was correlated to fasting plasma glucose level. So, the expression of different genes in SAT could be significantly increased the risk of diabetes mellitus in obese individuals (37). Hence in the present study, we analyzed the changes in FASN and PEPCK-C genes expression in SAT of obese patients with and without T2DM, and compared the results with those obtained from non-obese and non-diabetic subjects.

Regarding to FASN gene our data indicated that, there was over expression in mRNA of FASN gene in obese and diabetic obese groups than in controls. Furthermore, there was elevated in FASN expressions among obese diabetic group than obese non-diabetic group but without significant differences. We also conducted correlation analysis to determine if and to what degree the variability in metabolic factors explained FASN mRNA expressions and we observed an association between FASN gene and lipid profiles as well as insulin and HOMA-IR in obese diabetic group. This could be explained by the fact that insulin increases FASN expression and activity in human adipocytes, revealing that insulin sensitivity is important for their control and necessary for glucose absorption and conversion to triglycerides. In rat hepatocytes and adipocytes, insulin enhances the transcription of lipogenic genes; similar effect has also been seen in human adipocytes (38) thus, adiposity is more strongly associated with the development of insulin resistance and T2DM. Although FASN gene expression was significantly higher in obese vs lean individuals (39–41), it was shown that obese individuals' SAT expressed lower FASN mRNA than slim individuals exhibited (42). Additionally, FASN has been shown to be down-regulated with insulin resistance in obese rats (43), and had down-regulated among insulin resistant obese patients (44). In a study by Fernandez-Real et al. (45), the authors concluded that greater "circulatory" levels of FASN were associated with insulin resistance which may not be entirely accurate, as the same investigation revealed an inverse association between cellular and circulating FASN suggesting FASN exhaustion rather than up-regulation. Therefore, targeting FASN might be an impactful therapeutic approach in those obese individuals (46). Furthermore, FASN influenced the expression of transcription factors in genes related to diabetes in a beneficial manner (19). As a result, FASN may play a crucial role in the etiology of diabetes and insulin resistance. These findings established that FASN in islet cells is a crucial target for the treatment of diseases caused by islet dysfunction. The results of this study need to be confirmed in DM patients in order to assess the link between FASN gene expression and alterations of serum glucose in vivo (19). Herein our results found that FASN gene expression was positivity correlated to insulin and HOMA-IR in diabetic obese patients. It is well-known that, insulin resistance is related to both obesity and type 2 diabetes. Hyperinsulinemia developed as a result of increased beta cell activity associated with insulin resistance, which stimulates the release of more insulin to maintain normal glucose tolerance (34) and causes T2DM to develop (47). The function of beta cells and insulin secretion are compromised in obese individuals due to elevated levels of circulating fatty acids that are brought on by adipose tissues' restricted response (48). This finding could explain why obese individuals readily develop to T2DM.

Concerning to PEPCK, the data obtained demonstrated a considerably higher expression of this gene within obese groups with or without diabetes in comparison to the controls. While, there was no significant deference in PEPCK expressions between the two obese groups. Our results supported as the PEPCK-C enzyme catalyzes an irreversible step of gluconeogenesis and is therefore crucial for maintaining glucose homeostasis, as further recognized in laboratory mice which developed T2DM after PEPCK-C was overexpressed (20). Furthermore, prior review has revealed that overexpression of PEPCK-C boosts glyceroneogenesis and adipose tissue fat content. As consequence, glyceroneogenesis is essential to sustaining triacylglycerol reserves in adipose tissue and probably causes obesity (14). The result of current study is similarly to the prevailing view that the higher rates of gluconeogenesis and glucose production noted in patients with poorly managed T2DM are caused by increased transcription of PEPCK (49). Moreover, other investigators have demonstrated that PEPCK may have functions other than gluconeogenesis, such as controlling of triglyceride synthesis (50,51). Recently in this regard, PEPCK expression increased in obese diabetes rats, whereas it decreased in anti-diabetic groups (20). On the other hand, another study has revealed that in the hyperglycemia, there were no increases in the mRNA for PEPCK (52). Additionally, a previous study has reported, the PEPCK levels did not correlate strongly with gluconeogenesis in the mouse liver (53).

5. Conclusions

Our laboratory has assessed that PEPCK and FASN expressions are upregulated in obese patients with and without diabetes. Thus, FASN and PEPCK are variables that could play a role in the regulation and development of obese and obese diabetic cases, irrespective to diabetes status. Consequently, targeting subcutaneous adipose tissue for PEPCK and FASN inhibition may be a promising therapeutic strategy for the prevention and treatment of obesity and associated diabetes consequences. However, it is necessary to conduct more research to determine how obesity and diabetes are associated. Moreover, future intervention studies suggested to be explored the effects of potential treatments for obesity and obesity related diabetes through assessing the changes in FASN and PEPCK gene expression levels upon using specific treatments.

6. Limitations

There are a number of limitations to the current study that need to be considered. Firstly, the sample size was relatively small due to difficulties in obtaining consent and obtaining adipose tissue biopsies from the selected subjects. In addition, only subcutaneous fat that was separated from the abdomen was available, which is a quick and more easily obtained biopsy from normal and obese subjects during elective or programmed surgery. Therefore, our analyses were limited to subcutaneous adipose tissue samples. Finally, further larger-scale studies on different biological samples and different populations are required to clarify the associations of FASN and PEPCK genes in obesity susceptibility and its related diabetes.

7. Conflicts of interest
The authors declare that they have no conflicting interests.

8. Authors' contributions
All the authors have accepted responsibility for the entire content of this submitted manuscript and approved the submission.

9. Acknowledgments
We thank the National Research Centre for technical support for this study. The patients' participation in this study is much appreciated. We also acknowledge the assistance of the surgical crew in the sample collection.

10. Funding
Project funds (No. 12060170) from Egypt's National Research Centre (NRC) funded this work.

11. Ethical considerations
In compliance with protocol authorized by the Medical Research ethics committee at the Egyptian National Research Centre (No. 19-162), each subject gave written informed consent. The ethics committee authorized the study protocol, and all methods were employed in compliance with applicable laws, rules, and the Declaration of Helsinki.

12. References
1. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017;377(1):13-27. doi:10.1056/NEJMoa1614362
2. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. Nat Rev Genet. 2022;23(2):120-133. doi:10.1038/s41576-021-00414-z
3. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017;128:40-50. doi:10.1016/j.diabres.2017.03.024
4. Conte C, Fabbrini E, Kars M, Mittendorfer B, Patterson BW, Klein S. Multiorgan insulin sensitivity in lean and obese subjects. Diabetes Care. 2012;35(6):1316-1321. doi:10.2337/dc11-1951
5. Dilworth L, Facey A, Omoruyi F. Diabetes mellitus and its metabolic complications: The role of adipose tissues. Int J Mol Sci. 2021;22(14). doi:10.3390/ijms22147644
6. Aloke C, Egwu CO, Aja PM, et al. Current Advances in the Management of Diabetes Mellitus. Biomedicines. 2022;10(10):1-13. doi:10.3390/biomedicines10102436
7. Sethi JK, Vidal-Puig AJ. Thematic review series: adipocyte biology. Adipose tissue function and plasticity orchestrate nutritional adaptation. J Lipid Res. 2007;48(6):1253-1262. doi:10.1194/jlr.R700005-JLR200
8. Luo L, Liu M. Adipose tissue in control of metabolism. J Endocrinol. 2016;231(3):R77-R99. doi:10.1530/JOE-16-0211
9. Bhupathiraju SN, Hu FB. Epidemiology of Obesity and Diabetes and Their Cardiovascular Complications. Circ Res. 2016;118(11):1723-1735. doi:10.1161/CIRCRESAHA.115.306825
10. Scheen AJ, Van Gaal LF. Combating the dual burden: therapeutic targeting of common pathways in obesity and type 2 diabetes. lancet Diabetes Endocrinol. 2014;2(11):911-922. doi:10.1016/S2213-8587(14)70004-X
11. Davies GF, Khandelwal RL, Wu L, Juurlink BHJ, Roesler WJ. Inhibition of phosphoenolpyruvate carboxykinase (PEPCK) gene expression by troglitazone: a peroxisome proliferator-activated receptor-γ (PPARγ)-independent, antioxidant-related mechanism11Abbreviations: BADGE, bisphenol A diglycidyl ether; DCF, dichlorofl. Biochem Pharmacol. 2001;62(8):1071-1079. doi:10.1016/S0006-2952(01)00764-X
12. Ramnanan CJ, Edgerton DS, Cherrington AD. The Role of Insulin in the Regulation of PEPCK and Gluconeogenesis In Vivo. US Endocrinol. 2009;05(01):34. doi:10.17925/USE.2009.05.1.34
13. Franckhauser S, Muñoz S, Pujol A, et al. Increased fatty acid re-esterification by PEPCK overexpression in adipose tissue leads to obesity without insulin resistance. Diabetes. 2002;51(3):624-630. doi:10.2337/diabetes.51.3.624
14. Marcondes-de-Mello ML de F, Serafim-Costa MC, Alves-E-Silva MM, et al. Effect of glucocorticoids on glyceroneogenesis in adipose tissue: A systematic review. Biochimie. 2020;168:210-219. doi:10.1016/j.biochi.2019.11.007
15. Mobbs C V, Makimura H. Block the FAS, lose the fat. Nat Med. 2002;8(4):335-336. doi:10.1038/nm0402-335
16. Loftus TM, Jaworsky DE, Frehywot GL, et al. Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. Science. 2000;288(5475):2379-2381. doi:10.1126/science.288.5475.2379
17. Diraison F, Dusserre E, Vidal H, Sothier M, Beylot M. Increased hepatic lipogenesis but decreased expression of lipogenic gene in adipose tissue in human obesity. Am J Physiol Endocrinol Metab. 2002;282(1):E46-51. doi:10.1152/ajpendo.2002.282.1.E46
18. Gu C, She X, Zhou C, et al. Dihydroartemisinin ameliorates retinal vascular dysfunction in diabetes mellitus via the FASN/Kmal-mTOR/SREBP1 feedback loop. Pharmacol Res. 2021;174:105871. doi:10.1016/j.phrs.2021.105871
19. Wang K, Li L, Jin J, et al. Fatty acid synthase (Fasn) inhibits the expression levels of immune response genes via alteration of alternative splicing in islet cells. J Diabetes Complications. 2022;36(6):108159. doi:10.1016/j.jdiacomp.2022.108159
20. Elnagar A, El-Dawy K, El-Belbasi HI, et al. Ameliorative Effect of Oxytocin on FBN1 and PEPCK Gene Expression, and Behavioral Patterns in Rats' Obesity-Induced Diabetes. Front Public Heal. 2022;10(April):1-18. doi:10.3389/fpubh.2022.777129
21. Zhang K, Yang C, Zhou X, et al. TRIM21 ameliorates hepatic glucose and lipid metabolic disorders in type 2 diabetes mellitus by ubiquitination of PEPCK1 and FASN. Cell Mol Life Sci. 2023;80(6). doi:10.1007/s00018-023-04820-w
22. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res. 1998;6 Suppl 2:51S-209S. http://www.ncbi.nlm.nih.gov/pubmed/9813653

23. Chiang JL, Maahs DM, Garvey KC, et al. Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association. Diabetes Care. 2018;41(9):2026-2044. doi:10.2337/dci18-0023
24. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499-502. http://www.ncbi.nlm.nih.gov/pubmed/4337382
25. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-419. doi:10.1007/BF00280883
26. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. Methods. 2001;25(4):402-408. doi:10.1006/meth.2001.1262
27. Schleinitz D, Klöting N, Körner A, et al. Effect of Genetic Variation in the Human Fatty Acid Synthase Gene (FASN) on Obesity and Fat Depot-Specific mRNA Expression. Obesity. 2010;18(6):1218-1225. doi:10.1038/oby.2009.392
28. Assadi S, Shafiee SM, Erfani M, Akmali M. Antioxidative and antidiabetic effects of Capparis spinosa fruit extract on high-fat diet and low-dose streptozotocin-induced type 2 diabetic rats. Biomed Pharmacother. 2021;138:111391. doi:10.1016/j.biopha.2021.111391
29. Gao W, Liu JL, Lu X, Yang Q. Epigenetic regulation of energy metabolism in obesity. J Mol Cell Biol. 2021;13(7):480-499. doi:10.1093/jmcb/mjab043
30. Gouda W, Ahmed AEH, Mohamed AEHH, et al. Evaluation of the association of some circulating miRNA molecules in the metabolic syndrome. Qatar Med J. 2024;2024(4). doi:10.5339/qmj.2024.71
31. Nabawy M, Gouda W, Afify M, et al. Evaluation of some microRNAs dysregulation in obesity and obesity-related hypertension. Egypt Pharm J. 2025;24(2):199-206. doi:10.21608/epj.2025.407677
32. Gouda W, Eweida SM, Magdy H, et al. Role of MicroRNA in Obesity and Its Hypertension Complication. Jordan J Biol Sci. 2024;17(04):593-599. doi:10.54319/jjbs/170402
33. Barnett R. Obesity. Lancet. 2017;389(10069):591. doi:10.1016/S0140-6736(17)30273-8
34. Huang X, Liu G, Guo J, Su ZQ. The PI3K/AKT pathway in obesity and type 2 diabetes. Int J Biol Sci. 2018;14(11):1483-1496. doi:10.7150/ijbs.27173
35. Shawky T, Ahmed A, Gouda W, et al. Expressions of Micro-RNAs 365 and 375 in Obese Individuals suffering from Type 2 Diabetes. Egypt J Chem. Published online April 24, 2024:0-0. doi:10.21608/ejchem.2024.275827.9432
36. Nabawy M, Gouda W, El-Baz HA, et al. Impact of some miRNAs expression on induction of obesity related diseases. Egypt J Chem. Published online September 30, 2024:0-0. doi:10.21608/ejchem.2024.307399.10085
37. Aziz HA, Raslan M, El Dahshan D, Afify M, Hamimy WI, Gouda W. 11β Hydroxysteroid dehydrogenase type 1 Gene Expression in Obesity and its Complications. Egypt J Chem. 2023;66(7):165-174. doi:10.21608/EJCHEM.2022.157145.6819
38. Mayas MD, Ortega FJ, MacÍas-Gonzlez M, et al. Inverse relation between FASN expression in human adipose tissue and the insulin resistance level. Nutr Metab. 2010;7:1-7. doi:10.1186/1743-7075-7-3
39. Berndt J, Kovacs P, Ruschke K, et al. Fatty acid synthase gene expression in human adipose tissue: Association with obesity and type 2 diabetes. Diabetologia. 2007;50(7):1472-1480. doi:10.1007/s00125-007-0689-x
40. Blüher M, Michael MD, Peroni OD, et al. Adipose tissue selective insulin receptor knockout protects against obesity and obesity-related glucose intolerance. Dev Cell. 2002;3(1):25-38. doi:10.1016/s1534-5807(02)00199-5
41. Blüher M, Patti ME, Gesta S, Kahn BB, Kahn CR. Intrinsic heterogeneity in adipose tissue of fat-specific insulin receptor knock-out mice is associated with differences in patterns of gene expression. J Biol Chem. 2004;279(30):31891-31901. doi:10.1074/jbc.M404569200
42. Turner SM, Roy S, Sul HS, et al. Dissociation between adipose tissue fluxes and lipogenic gene expression in ob/ob mice. Am J Physiol Endocrinol Metab. 2007;292(4):E1101-9. doi:10.1152/ajpendo.00309.2005
43. Eissing L, Scherer T, Tödter K, et al. De novo lipogenesis in human fat and liver is linked to ChREBP-β and metabolic health. Nat Commun. 2013;4:1528. doi:10.1038/ncomms2537
44. Sievert H, Krause C, Geißler C, et al. Epigenetic Downregulation of FASN in Visceral Adipose Tissue of Insulin Resistant Subjects. Exp Clin Endocrinol Diabetes. 2021;129(09):674-682. doi:10.1055/a-1150-7446
45. Fernandez-Real JM, Menendez JA, Moreno-Navarrete JM, et al. Extracellular Fatty Acid Synthase: A Possible Surrogate Biomarker of Insulin Resistance. Diabetes. 2010;59(6):1506-1511. doi:10.2337/db09-1756
46. Wu Z, Zhu L, Nie X, Liu Y, Zhang X, Qi Y. Inhibition of fatty acid synthase protects obese mice from acute lung injury via ameliorating lung endothelial dysfunction. Respir Res. 2023;24(1):1-18. doi:10.1186/s12931-023-02382-w
47. Oliveira JM, Rebuffat SA, Gasa R, Gomis R. Targeting type 2 diabetes: lessons from a knockout model of insulin receptor substrate 2. Can J Physiol Pharmacol. 2014;92(8):613-620. doi:10.1139/cjpp-2014-0114
48. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444(7121):840-846. doi:10.1038/nature05482
49. Burgess SC, He T, Yan Z, et al. Cytosolic phosphoenolpyruvate carboxykinase does not solely control the rate of hepatic gluconeogenesis in the intact mouse liver. Cell Metab. 2007;5(4):313-320. doi:10.1016/j.cmet.2007.03.004
50. Reshef L, Olswang Y, Cassuto H, et al. Glyceroneogenesis and the triglyceride/fatty acid cycle. J Biol Chem. 2003;278(33):30413-30416. doi:10.1074/jbc.R300017200
51. She P, Burgess SC, Shiota M, et al. Mechanisms by which liver-specific PEPCK knockout mice preserve euglycemia during starvation. Diabetes. 2003;52(7):1649-1654. doi:10.2337/diabetes.52.7.1649
52. Samuel VT, Beddow SA, Iwasaki T, et al. Fasting hyperglycemia is not associated with increased expression of PEPCK or G6Pc in patients with type 2 diabetes. Proc Natl Acad Sci U S A. 2009;106(29):12121-12126. doi:10.1073/pnas.0812547106
53. Méndez-Lucas A, Duarte JAG, Sunny NE, et al. PEPCK-M expression in mouse liver potentiates, not replaces, PEPCK-C mediated gluconeogenesis. J Hepatol. 2013;59(1):105-113. doi:10.1016/j.jhep.2013.02.020