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The association of PTEN/PI3K/Akt pathway gene expression with insulin indices in adipose tissues of non-diabetic female adults: a cross-sectional study

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Insulin resistance (IR) is a complex metabolic condition that serves as a common thread connecting type 2 diabetes (T2DM), metabolic syndrome (MetS), cardiovascular disease (CVD), and even certain cancer outcomes. Understanding and addressing IR is crucial for the prevention and management of these interrelated health challenges. Adipose tissue (AT) is one of the main targets for insulin action, and insulin suppresses lipolysis in this tissue. This study aimed to investigate the relationship between genes in the PI3K/AKT pathway and the negative regulator of this pathway, PTEN, with indices of insulin resistance in human adipose tissue. In this cross-sectional study, 118 women, aged ≥ 18 years were selected among patients who were admitted to hospitals (Mostafa Khomeini and Khatam Al-Anbia, Tehran, Iran) for elective and minimal abdominal surgery including appendectomy and umbilical and inguinal hernia repair. Anthropometric and laboratory parameters, physical activity, and dietary intake were measured. Expression of PTEN, PI3K, and Akt genes were evaluated using Real-Time qRT-PCR. Insulin-related metabolic indices such as hyperinsulinemia, HOMA-IR, HOMA-B, HOMA-S, QUICKI, and TyG indexes were defined and calculated. After controlling age, physical activity, BMI, and energy intake, the expression of SAT PTEN was negatively associated with IR (β=-4.475, *P* = 0.021) and positively associated with HOMA-B cell dysfunction (β = 4.944, *P* = 0.012). VAT PI3K was positively associated with hyperinsulinemia (β = 8.802, *P* = 0.008) and IR (β = 7.710, *P* = 0.028). Higher VAT Akt gene expression was associated with higher hyperinsulinemia (β = 6.684, *P* = 0.003) and IR (β = 5.296, *P* = 0.027). Moreover, higher SAT Akt mRNA level was associated with FPI (β = 0.128, *P* = 0.048), and hyperinsulinemia (β = 4.201, *P* = 0.008). The findings of the present study suggest that hyperinsulinemia and insulin resistance (HOMA-IR), are directly associated with PI3K and Akt expression yet they show an inverse relationship with PTEN, which inhibits the insulin pathway.

Keywords Phosphatase and tensin homologue, Phosphatidylinositol-3-kinase, AKT serine/Threonine kinase, Insulin resistance, Adipose tissues, Females

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Insulin resistance (IR) is a condition in which insulin, despite having sufficient or even elevated concentration in the circulation, is unable to stimulate the cells to uptake glucose. Under normal conditions, insulin stimulates glucose uptake by binding to its specific receptors on the surface of target cells, mainly GLUT4, in adipose tissue and skeletal muscles, thus playing a key role in blood sugar regulation. Abnormalities in insulin signaling pathways can decrease insulin sensitivity, resulting in IR[1].

Insulin resistance is a complex metabolic condition that serves as a common thread connecting type 2 diabetes (T2DM), metabolic syndrome (MetS), cardiovascular disease (CVD), and even certain cancer outcomes[2]. Insulin resistance is a complex trait, and while environmental factors, including lifestyle, are effective in its occurrence, genes also play a decisive role in its development[3,4]. Recent studies have highlighted the importance of adipose tissue in the development of IR, as it may release lipids and other circulating factors that establish IR in other tissues[5].

White adipose tissue is divided into two main depots, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). SAT and VAT are different in rates of insulin-stimulated glucose uptake[6], sensitivity to lipolysis[7], endocrine properties[8], and their sensitivity to IR[9].

The basis of IR is the alterations in the mechanisms of the insulin receptor function and signal transduction[10]. The phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway plays a fundamental role in normal cellular processes involved in growth and metabolism and also in processes maintaining glucose homeostasis and regulating fat metabolism[11,12]. Insulin, the primary ligand for PI3K, binds to its receptors, which in turn activates the PI3K/Akt signaling pathway. This activation leads to increased glucose transporters, primarily in skeletal muscle cells and adipocytes. Obviously, dysregulation of this pathway results in the development of IR[12].

PTEN (phosphatase and tensin homologue) is known as the main insulin pathway regulator[13]. PTEN acts as an upstream regulator for the PI3K/Akt pathway and negatively regulates the signaling pathway[14]. Research has highlighted PTEN's significant involvement in adipose tissue biology, particularly in the regulation of adipocyte progenitor proliferation, differentiation, and overall adipose tissue homeostasis[15]. Studies have demonstrated that reduced PTEN expression enhances both the proliferation and differentiation capacity of adipocyte progenitors, partially through increased activation of the PI3K/Akt pathway[16]. Tissue-specific PTEN knockout in mouse models and inhibition of PTEN mRNA translation by miR-26b, in VAT from obese rodent models and obese human subjects, activate the PI3K pathway and enhance insulin sensitivity in adipocytes[17]. On the other hand, PTEN haploinsufficiency in humans causes a profound constitutive insulin sensitivity and obesity[18].

In this cross-sectional study, we aimed to investigate the association between PTEN/PI3K/Akt pathway gene expression and IR-related indices in adipose tissues of non-diabetic adults. Our findings may provide insights into the molecular mechanisms underlying IR and identify potential therapeutic targets for the prevention and treatment of metabolic disorders.

Materials and methods

Participants selection

In this cross-sectional study, 118 women, aged ≥ 18 years were selected among patients who were admitted to hospitals (Mostafa Khomeini and Khatam Al-Anbia, Tehran, Iran) for elective and minimal abdominal surgery including appendectomy and umbilical and inguinal hernia repair between 2012 and 2015. Participants who had cancer, with history of diabetes mellitus, or taking hypoglycemic, lipid-lowering, or anti-obesity drugs were excluded. Moreover, individuals with pregnancy and lactation or hospitalization less than two days before surgery were also excluded. Written informed consent was obtained from all the participants. The Ethics Committee of the Research Institute approved this research for Endocrine Sciences (RIES) of Shahid Beheshti University of Medical Sciences (IR.SBMU.ENDOCRINE.REC.1403.039). Research was conducted following the Declaration of Helsinki and RIES institutional guidelines.

Data collection

Before surgery, data such as anthropometrics, demographics including age, medical history, drug usage (hypoglycemic drugs, lipid-lowering drugs, hypertension drugs, heart drugs, hormonal drugs, and supplements), dietary intakes, and PA were asked and recorded. Besides, 5 ml of blood samples (10–12 h overnight fasting) were collected in potassium EDTA-containing tubes and plasma was separated for biochemistry measurements. During the elective surgery, 50–100 mg of adipose tissues, SAT was harvested from the 5 cm periumbilical area; VAT was collected from the upper left part of omentum (subomental) fat, directly frozen in liquid nitrogen, and stored at -80 °C.

Anthropometric and laboratory parameters and blood pressure measurements

All anthropometric characteristics, including weight, height, and waist, hip, and neck circumferences were measured according to standard protocols described in detail previously[19]. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). All plasma were gathered after centrifuging the fasting blood samples at 3000×*g* for 5 min and biochemical components, including fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), and insulin levels, were measured as described previously[20]. Inter-and intra-assay coefficients of variation (CV) for all of them were both < 5%. After 15 min of rest, systolic and diastolic blood pressures (SBP and DBP) were measured twice in one-minute intervals with a mercury sphygmomanometer, and their average was recorded[19].

Physical activity assessment

Participants' habitual physical activity (PA) during seven days was assessed by trained interviewer using the validated International Physical Activity Questionnaire (IPAQ)-long-form[21], which has demonstrated reliability,

validity, and reproducibility in Iranian populations[22]. The IPAQ data was converted into metabolic equivalent (MET) minutes per week. This approach yielded a total MET score for each participant.

Dietary intake assessment

Regular dietary intakes of the participants was collected by an experienced interviewer using a valid and reliable semi-quantitative 147 item food frequency questionnaire (FFQ)[23]. We used the United States Department of Agriculture (USDA) food composition table (FCT) to compute the daily energy and nutrient intake. The reliability and validity of the FFQ, evaluated in a previous study against twelve 24-h dietary recalls and biomarkers, indicated that it provides reasonably valid measures of the average long-term dietary intakes[24].

Evaluation of PTEN/PI3K/Akt pathway in human adipose tissues using Real-Time qRT-PCR

Adipose tissue samples (SAT and VAT) were weighted (30–50 mg), incised, and homogenized in 1 mL TRIzol reagent (Invitrogen, USA, Cat. No.: 15596-026) for total RNA extraction according to the manufacturer's protocol[25]. Proteins, lipids, carbohydrates, and cell debris were eliminated through the extraction of the aqueous. DNase I was used to remove traces of genomic DNA. The quality and quantity of extracted RNA were measured by determining the absorbance ratio at 260 and 280 nm (*A260/280*) using a Nanodrop spectrophotometer (ND-1000, USA) and gel electrophoresis, respectively. Total complementary DNA (cDNA) was synthesized from total RNA according to the instructions for the cDNA synthesis kit (BIOFACT, South Korea) and stored at -20 °C for later use. The primer sequences of PTEN, PI3K, Akt, and GAPDH (internal control gene[19,26] were provided in previous studies[27–29].

The Real-time quantitative reverse transcription-polymerase chain reaction (qRT PCR) assay was performed using the SYBR-Green PCR Master Mix (BioFact, Korea) in a Corbett Rotor-Gene 6000 machine (Sydney, Australia). The qPCR was performed in 20 µL volumes and the cycling programs were provided previously[27,28]. Duplicate reactions were performed for each sample. Relative quantitation of mRNA expression was performed using the comparative CT method, according to Livak et al.[30]. All qRT-PCR laboratory procedures followed the MIQE guidelines[31].

Calculation and definition of insulin indices

Hyperinsulinemia was defined as fasting insulin (µU/mL) ≥ 11.13 for females[32]. Original HOMA models were calculated as HOMA-IR=[fasting insulin (µU/mL)×fasting glucose (mmol/L)]/22.5, beta-cell function (HOMA-B)=[20×fasting insulin (µU/mL)]/[fasting glucose (mmol/L)-3.5][33], and HOMA-S = 1/HOMA-IR×100[34,35]. HOMA-B cell dysfunction also was shown as HOMA-B ≤ 86.2 for females[32]. The quantitative insulin-sensitivity check index (QUICKI) was calculated based on the formula proposed by Katz et al.[36] = 1/[log(fasting insulin (µU/mL) + log(fasting glucose (mg/dL)]. Participants with HOMA-IR ≥ 1.85 for females was considered to be IR[32]. The Triglyceride-Glucose index (TyG-index) was calculated as Ln [fasting TG (mg/dL)×FPG (mg/dL)/2][37].

Data statistical analysis

Data were analyzed using SPSS version 26, and statistical differences were considered significant at $P\ value < 0.05$. The Kolmogorov–Smirnov test was used to evaluate the distribution of variables. Normally distributed variables were expressed as mean ± standard deviation (SD), and non-normal variables were reported as median (interquartile 25, 75). The Chi-Square test was used to compare qualitative variables and the Mann–Whitney U test for variables with non-normal distribution. Spearman's correlation coefficients were determined between PTEN, PI3K, and Akt expression and IR indices in the SAT and VAT. Comparative graphs of relative expression were drawn with SPSS software with Mean ± 1SEM. The association of gene expression and insulin-related metabolic indices in VAT and SAT was assessed using linear regression analysis. Sex, age, BMI, physical activity, and energy intake (kcal) were included as confounding variables and adjusted in the model. These variables were selected based on epidemiological guidelines and their established roles in health studies: age is a fundamental confounder due to its correlation with physiological changes, disease risk, and lifestyle factors; BMI serves as both a mediator and confounder in studies of energy balance; energy intake is crucial for distinguishing diet-disease relationships from total caloric consumption; and physical activity is a key modifier of energy expenditure that directly interacts with both BMI and energy intake[38,39].

Results

General anthropometric and biochemical characteristics

The general anthropometric and biochemical characteristics of the study participants are summarized in Table 1. The average age of the individuals was 38.8 ± 11.7 years. Among the participants, 45.8% exhibited hyperinsulinemia and 33.1% showed HOMA-B cell dysfunction. The median values (interquartile range) for key IR-related indices were as follows: HOMA-IR, 2.3(1.1, 4.9); HOMA-B, 139.1(72.6, 268.8); HOMA-S, 42.6(20.6, 91.4); QUICKI, 0.1(0.1, 0.2); and TyG index, 8.4(8.0, 8.8).

Correlations between gene expression and insulin-related metabolic indices

Spearman's correlation coefficients assessing the relationship between PTEN, PI3K, and Akt gene expression and insulin-related metabolic indices in adipose tissues are provided in Table 2.

Significant positive correlations were observed between PI3K mRNA levels and both FPI and HOMA-IR ($P < 0.05$). Similarly, Akt mRNA levels showed significant positive correlations with FPI and HOMA-IR ($P < 0.05$). Conversely, VAT PI3K and Akt mRNA levels were negatively correlated with HOMA-S and QUICKI, indicating an inverse relationship with insulin sensitivity.

Variables	Total ($N=118$)	Without IR ($N=52$)	With IR ($N=66$)	P value
Age (year)	38.8 ± 11.7	42.1 ± 12.0	36.2 ± 10.8	0.007
Waist circumferences (cm)	107.0 ± 21.8	99.2 ± 22.7	113.1 ± 19.1	< 0.001
Body mass index (kg/m2)	38.2(26.5, 45.3)	29.0(24.3, 40.2)	42.4(34.3, 46.3)	< 0.001
Fasting plasma glucose (mg/dL)	89.0(79.0, 97.0)	84.9(74.0, 93.0)	92.5(85.0, 104.8)	0.001
Fasting plasma triglycerides (mg/dL)	98.0(68.0, 148.3)	80.0(65.3, 125.0)	119.5(72.0, 159.7)	0.002
Fasting plasma insulin (munit/ml)	10.5(5.4, 21.1)	5.25(3.19, 6.35)	19.7(12.2, 25.5)	< 0.001
Fasting plasma cholesterol (mg/dL)	181.8 ± 39.6	181.1 ± 43.5	182.4 ± 36.5	0.862
Systolic blood pressure (mmHg)	110.0(110.0, 120.0)	110.0(110.0, 120.0)	110.0(110.0, 120.0)	0.943
Diastolic blood pressure (mmHg)	70.0(70.0, 80.0)	72.5(70.0, 80.0)	70.0(66.3, 80.0)	0.563
Hyperinsulinemia (%)	54(45.8)	0.0(0.0)	54(81.8)	< 0.001
HOMA-B cell dysfunction (%)	39(33.1)	34(65.4)	5(7.6)	< 0.001
HOMA-IR	2.3(1.1, 4.9)	1.02(0.65, 1.33)	4.49(2.71, 5.87)	< 0.001
HOMA-B	139.1(72.6, 268.8)	75.4(32.2, 108.7)	223.6(161.1, 342.2)	< 0.001
HOMA-S	42.6(20.6, 91.4)	98.6(75.3, 154.6)	22.3(17.0, 36.9)	< 0.001
QUICKI	0.1(0.1, 0.2)	0.17(0.16, 0.18)	0.13(0.13, 0.14)	< 0.001
TyG-index	8.4(8.0, 8.8)	8.09(7.90, 8.51)	8.69(8.13, 8.93)	< 0.001
Total energy intake (kcal)	2665.3(2162.7, 3423.4)	2479.5(2026.0, 3533.2)	2699.5(2277.5, 3361.7)	0.332
Total physical activity (MET-min/week)	700.0(185.8, 1671.0)	903.0(317.3, 2024.3)	583.0(111.3, 1535.6)	0.206

Table 1. General anthropometric and biochemical characteristics of the participants. HOMA: homeostasis model assessment; QUICKI: quantitative insulin sensitivity check index. Data were defined as mean ± standard deviation, median (25, 75th interquartile), percentage (%).

	FPG		FPI		HOMA-IR		HOMA-B		HOMA-S		TyG-index		QUICKI	
	r	P value	r	P value	r	P value	r	P value	r	P value	r	P value	r	P value
Visceral														
PTEN	-0.059	0.525	-0.121	0.193	-0.117	0.207	0.005	0.954	0.117	0.207	-0.041	0.659	0.117	0.207
PI3K	0.055	0.556	0.211	0.022	0.211	0.022	0.097	0.295	-0.211	0.022	0.087	0.350	-0.211	0.022
Akt	0.024	0.796	0.208	0.024	0.195	0.034	0.127	0.169	-0.195	0.034	0.007	0.940	-0.195	0.034
Subcutaneous														
PTEN	-0.085	0.361	-0.266	0.004	-0.259	0.005	-0.196	0.033	0.259	0.005	-0.059	0.527	0.259	0.005
PI3K	0.045	0.626	0.022	0.813	0.023	0.801	-0.061	0.508	-0.023	0.801	0.164	0.077	-0.023	0.801
Akt	0.070	0.453	0.161	0.082	0.150	0.106	0.019	0.841	-0.150	0.106	0.105	0.258	-0.150	0.106

Table 2. Spearman's correlation coefficients between PTEN, PI3K, and Akt expression and Insulin-related metabolic indices in the adipose tissues. FPG, fasting plasma glucose; FPI, fasting plasma insulin; IR, insulin resistance. *Correlation is significant at the 0.05 level (2-tailed).

PTEN expression in SAT was significantly negatively correlated with FPI, HOMA-IR, and HOMA-B ($P<0.05$). In contrast, PTEN levels positively correlated with HOMA-S and QUICKI, markers of improved insulin sensitivity ($P<0.05$).

Differential gene expression according to insulin-related metabolic indices

Figure 1 illustrates that participants with hyperinsulinemia exhibited significantly lower relative PTEN expression in SAT compared to those without hyperinsulinemia (median 0.86 vs. 2.73, $P=0.019$). Similarly, women with IR showed reduced SAT PTEN expression compared to insulin-sensitive individuals (median 0.89 vs. 2.73, $P=0.016$). Interestingly, PTEN expression was higher in participants with HOMA-B cell dysfunction (median 3.4 vs. 1.20, $P=0.018$).

In VAT, PI3K gene expression was significantly elevated in groups with hyperinsulinemia and IR (median 1.50 vs. 1.21, $P=0.006$; 1.47 vs. 1.25, $P=0.032$, respectively) (Fig. 2). Likewise, Akt expression in VAT was higher in individuals with hyperinsulinemia (median 1.86 vs. 1.03, $P=0.002$) and IR (median 1.60 vs. 1.03, $P=0.021$) (Fig. 3).

Associations between gene expression and insulin-related metabolic indices: linear regression analysis

To further elucidate the association of PTEN, PI3K, and Akt genes expression and insulin-related metabolic indices, linear regression analysis were conducted for VAT and SAT, adjusting for potential confounders including age, physical activity, BMI, and energy intake (kcal). The results are presented in Tables 3 and 4, and 5.

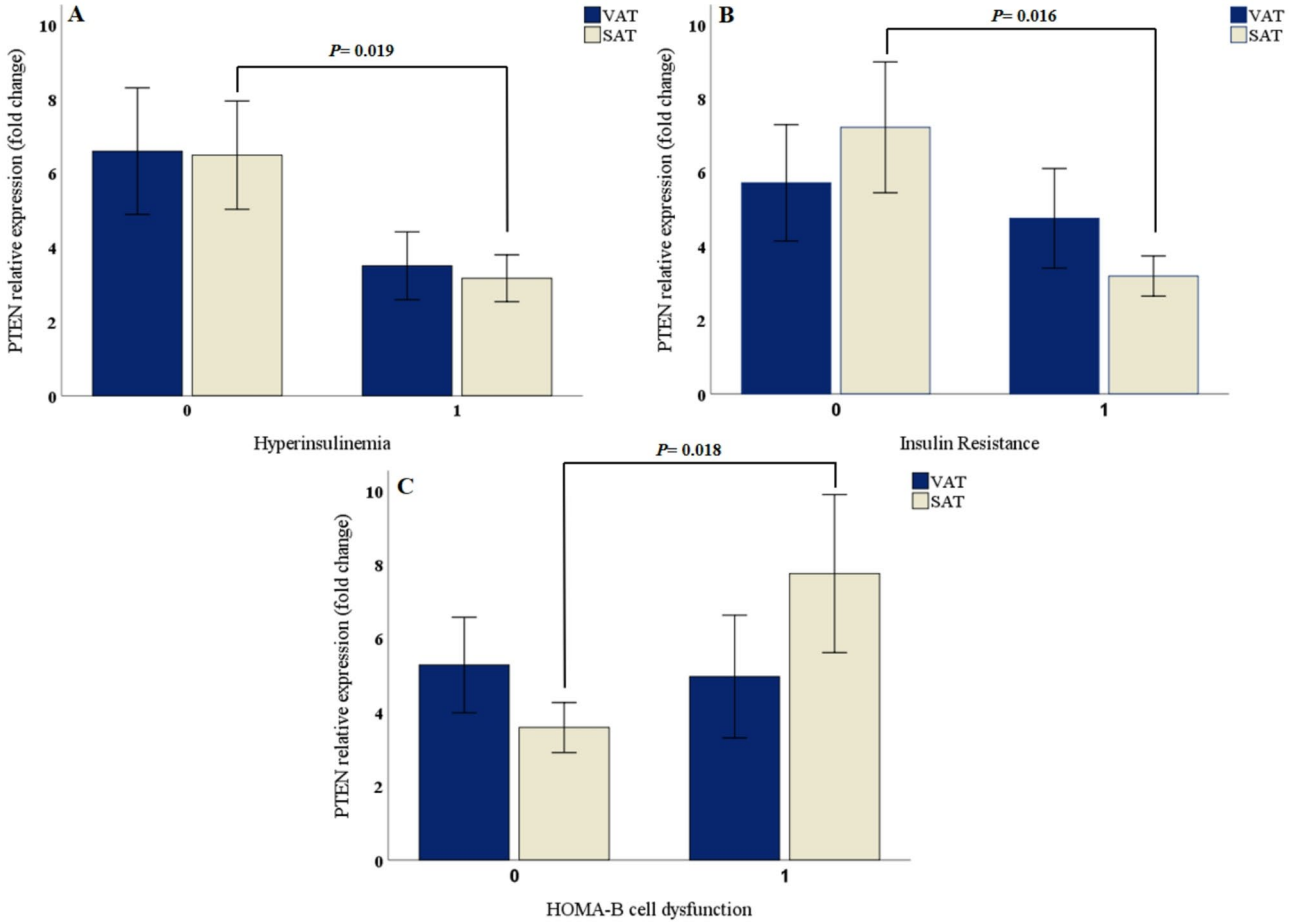

Fig. 1. Comparison of relative expression of PTEN gene in visceral adipose tissues (VAT) and subcutaneous adipose tissue (SAT) of (**A**), females with and without hyperinsulinemia (**B**), females with and without insulin resistance (**C**), and females with and without HOMA-B cell dysfunction. Error bars were defined as 1 standard error of the mean. 0 is referred to without and 1 is referred to with. The displayed P values were obtained from the Mann–Whitney U test to compare the differences between the two groups.

After adjustment, SAT PTEN expression was significantly negatively associated with IR (β=-4.475, 95%CI (-8.270, -0.681); $P=0.021$), indicating that lower PTEN expression corresponds to higher IR. Conversely, SAT PTEN was positively associated with HOMA-B cell dysfunction (β = 4.944, 95%CI (1.115, 8.773); $P=0.012$) (Table 3).

VAT PI3K expression showed significant positive associations with hyperinsulinemia (β = 8.802, 95%CI (2.338, 15.265); $P=0.008$) and IR (β = 7.710, 95%CI (0.831, 14.589), $P=0.028$), indicating that increased PI3K expression in VAT may be linked to worsening IR (Table 4).

Elevated VAT Akt expression was significantly associated with hyperinsulinemia (β = 6.684, 95%CI (2.316, 11.053); $P=0.003$) and IR (β = 5.296, 95%CI (0.610, 9.982); $P=0.027$). Additionally, higher SAT Akt mRNA levels were positively associated with FPI (β = 0.128, 95%CI (0.001, 0.256); $P=0.048$) and hyperinsulinemia (β = 4.201, 95%CI (1.118, 7.284); $P=0.008$) (Table 5).

Discussion

The results of the current cross sectional study on 118 women, aged ≥ 18 years, showed a negative correlation between PTEN gene expression in subcutaneous fat tissue and IR. Meanwhile, PI3K and Akt expression had a significant association with IR in viceral adipose tissue. There was also a significant positive correlation of PI3K and Akt gene expression with fasting plasma insulin levels and HOMA-IR measures in VAT.

In the present study, higher fasting serum insulin levels and HOMA-IR index were found to be positively correlated with increased expression of genes involved in the insulin signaling pathway, including PI3K and Akt, in VAT. These findings were observed in a study population comprising overweight and obese individuals with a median BMI of 38.2, who nevertheless exhibited relatively favorable biochemical and metabolic profiles. The elevated insulin levels in these individuals are likely related to their obesity, which results from a complex interplay of environmental and genetic factors. The observed upregulation of PI3K and Akt genes, together with the downregulation of the PTEN gene, may reflect an adaptive response to increased insulin levels in this

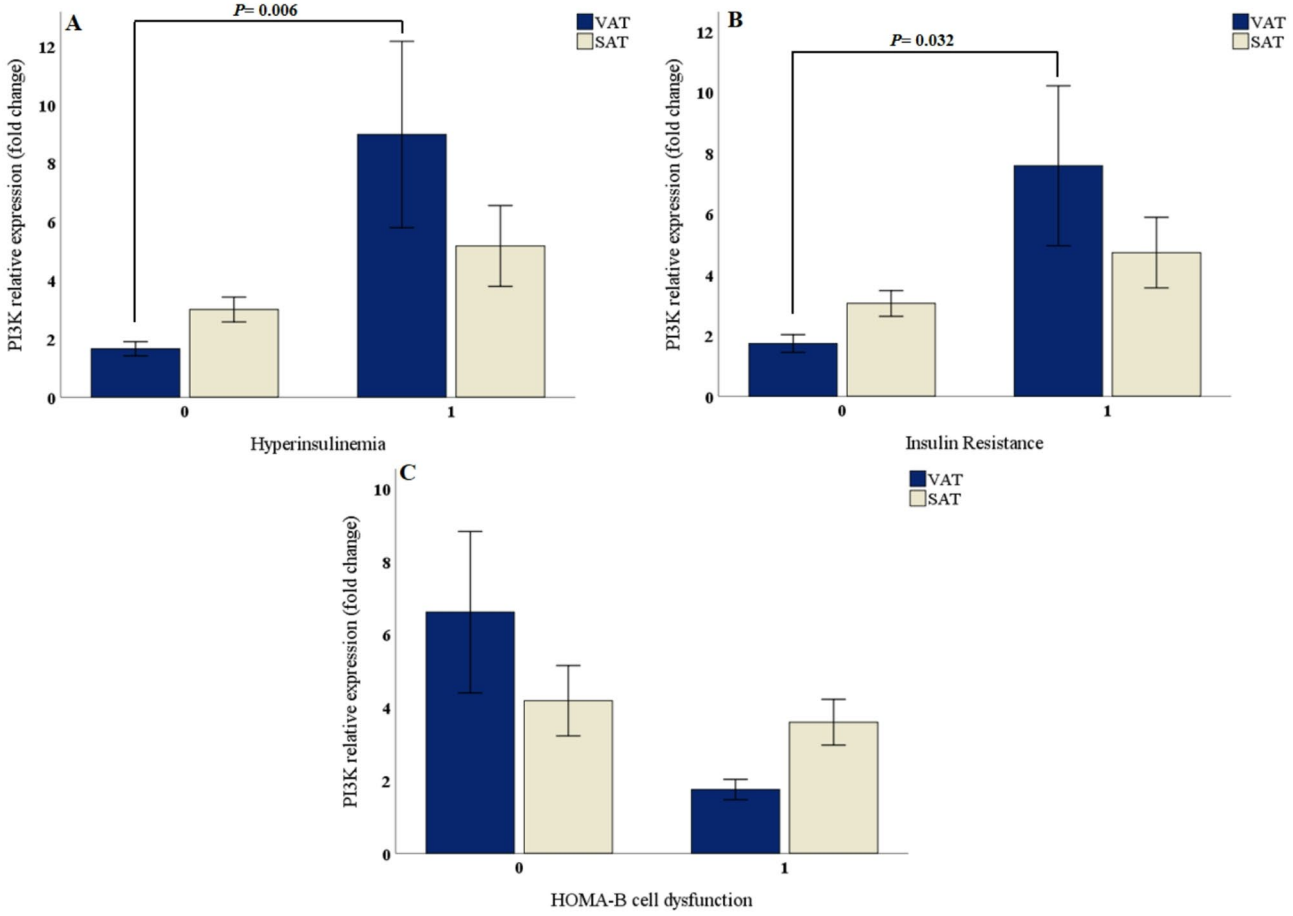

Fig. 2. Comparison of relative expression of PI3K gene in visceral adipose tissues (VAT) and subcutaneous adipose tissue (SAT) of (**A**), females with and without hyperinsulinemia (**B**), females with and without insulin resistance (**C**), and females with and without HOMA-B cell dysfunction. Error bars were defined as 1 standard error of the mean. 0 is referred to without and 1 is referred to with. The displayed P values were obtained from the Mann–Whitney U test to compare the differences between the two groups.

population. Such changes in gene expression could potentially influence glucose uptake and insulin dynamics in adipose tissue, although the precise physiological implications require further investigation.

Regarding HOMA-IR, it is essential to note its direct correlation with blood sugar and serum insulin, given its calculating formula. In the current study, it appears to be predominantly influenced by higher insulin levels, as most participants had normal blood sugar levels. Consequently, the elevated HOMA-IR levels in the majority of study participants primarily indicate higher insulin levels. Therefore, it is not surprising that both insulin and HOMA-IR in this study have shown a positive relationship with the expression of downstream genes involved in insulin's normal regulatory pathway.

Insulin is an important regulator of adipogenesis and adipocyte survival. Via binding to insulin receptor on adipocytes membrane, activates PI3K/AKT signaling pathway that promotes fatty acid synthesis and glucose uptake in adipose tissue[40]. PTEN, a protein that inhibits the AKT signaling pathway, can regulate the process of adipogenesis via inhibiting the transcription factor FOXO-1. Inhibition of FOXO-1 leads to the activation of another transcription factor called PPAR-γ. PPAR-γ is a master adipogenic factor that drives the development of mature fat cells. Thus; PTEN-AKT-FOXO-1 axis regulates adipogenesis through regulating the activity of PPAR-γ[41,42]. In a study conducted by Daneshafrooz et al. (2022), on the same population the relationship between Omentin gene expression and IR indicators was evaluated. The study subjects included 91 healthy individuals and 46 individuals with IR, defined by a HOMA-IR index ≥ 3.2. Their results showed that Omentin gene expression in subcutaneous fat tissue had a positive relationship with fasting plasma insulin and the HOMA-IR index, and a significant negative relationship with the HOMA-B index[43]. Omentin is an adipokine selectively expressed in VAT and is abundant in plasma. It has been reported to modulate insulin sensitivity[44]. Omentin plays a significant role in the activation of the PI3K/Akt signaling pathway[45], whereas PTEN acts as an inhibitor of this pathway. Our results are consistent with previous reports indicating that the expression of omentin and PTEN are the opposite.

Our findings reveal distinct associations between the expression of key insulin signaling genes- PTEN, PI3K, and Akt in SAT and VAT, and various insulin-related metabolic indices. Notably, higher PTEN expression in SAT was inversely associated with IR but positively correlated with HOMA-B, an indicator of β-cell function.

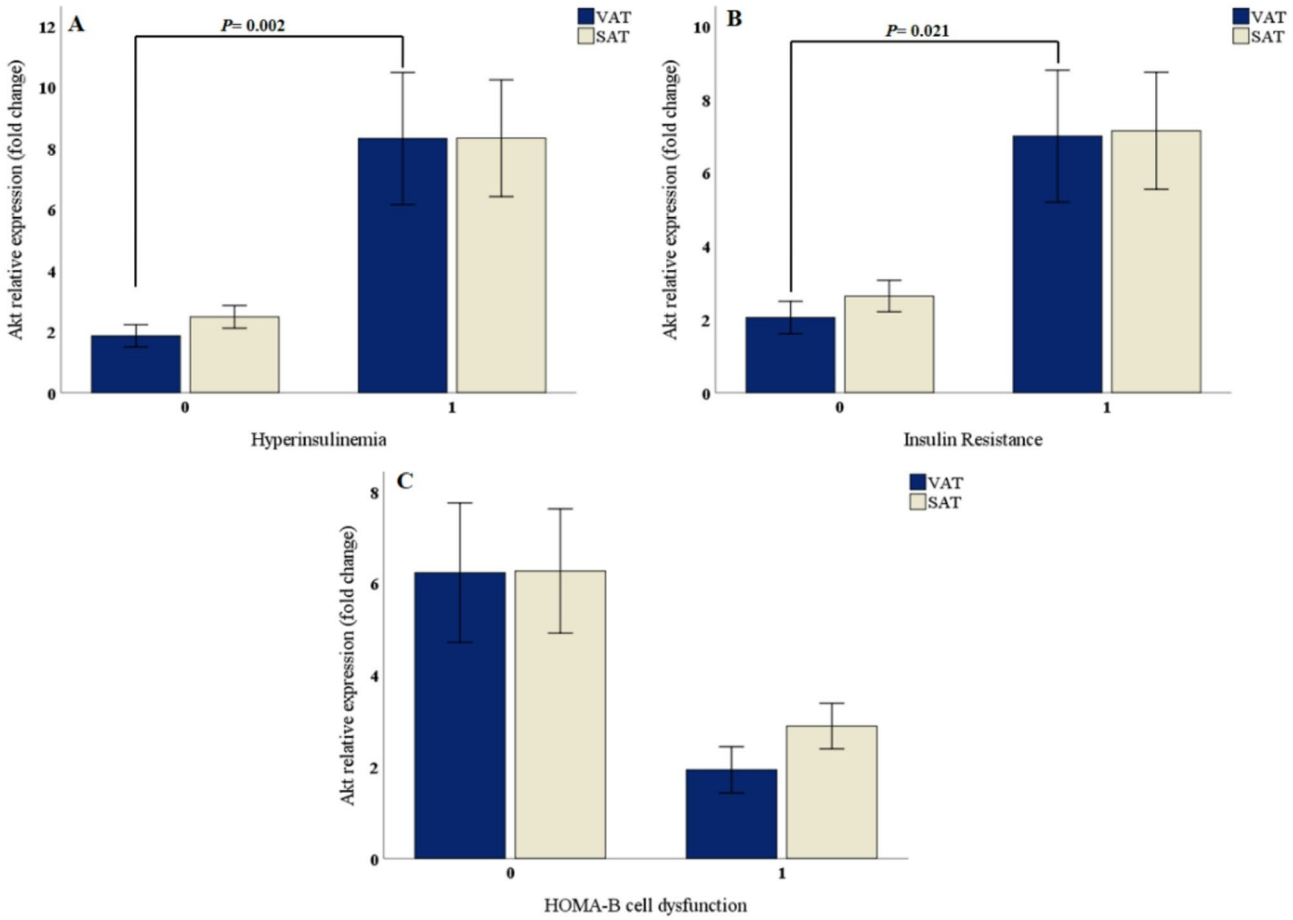

Fig. 3. Comparison of relative expression of Akt gene in visceral adipose tissues (VAT) and subcutaneous adipose tissue (SAT) of (**A**), females with and without hyperinsulinemia (**B**), females with and without insulin resistance (**C**), and females with and without HOMA-B cell dysfunction. Error bars were defined as 1 standard error of the mean. 0 is referred to without and 1 is referred to with. The displayed P values were obtained from the Mann–Whitney U test to compare the differences between the two groups.

This suggests that increased PTEN expression may reflect a regulatory mechanism aimed at modulating insulin signaling sensitivity in subcutaneous fat, potentially influencing pancreatic β-cell compensation. Conversely, elevated PI3K and Akt gene expression in VAT was positively associated with hyperinsulinemia and IR, indicating that upregulation of these signaling components may be a compensatory response to impaired insulin sensitivity in visceral fat depots. Collectively, these results underscore the complex, depot-specific regulation of insulin signaling pathways in adipose tissue and support the metabolic differences between SAT and VAT[46].

The early and primary compensatory response to IR is β-cell adaptation (hyperplasia or increased insulin secretion in β-cells), which occurs to maintain normoglycemia for a short time[47]. Prolonged IR resulted in ambient hyperglycemia, high levels of free fatty acids, and inflammatory cytokines, which potentially could damage β-cell function and drive β-cell exhaustion[48].

Adipose tissue also exhibits compensatory upregulation of several signaling pathways to maintain metabolic balance in the context of IR. As insulin sensitivity declines, adipocytes and resident immune cells in VAT engage in complex crosstalk, leading to increased secretion of pro-inflammatory cytokines and activation of pathways such as MAPK signaling[49]. This inflammatory milieu not only perpetuates IR but also triggers adaptive responses, including enhanced insulin secretion (hyperinsulinemia) and upregulation of key signaling molecules like PI3K and Akt, as observed in this study. These compensatory mechanisms aim to counteract impaired glucose uptake and maintain energy homeostasis, but they may also exacerbate local inflammation and metabolic dysfunction over time[50].

Considering the differences between human and rodent biology, a strength of our study is the use of human samples, which helps shed light on possible genes for managing IR. To the best of our knowledge and according to the literature, this is the first human study demonstrating the association between the PTEN/PI3K/AKT pathway and insulin-related metabolic indices in VAT and SAT among non-diabetic individuals. Furthermore, all covariates were gathered during interviews instead of self-reports, which increases the credibility of the data.

A few limitations of our study should be mentioned. The primary limitation is that we used samples from patients who were already admitted to the hospital for surgery rather than employing a random sampling

	Visceral adipose tissue			Subcutaneous adipose tissue		
	β (95% confidence interval)	STZ β	*P* value	β (95% confidence interval)	STZ β	*P* value
Fasting plasma glucose						
Model 1	-0.028(-0.148, 0.092)	-0.043	0.645	-0.023(-0.124, 0.078)	-0.043	0.648
Model 2	-0.038(-0.159, 0.083)	-0.059	0.536	-0.019(-0.121, 0.083)	-0.035	0.714
Model 3	-0.053(-0.178, 0.073)	-0.082	0.408	-0.044(-0.146, 0.058)	-0.081	0.398
Fasting plasma insulin						
Model 1	-0.084(-0.263, 0.095)	-0.090	0.354	-0.146(-0.294, 0.003)	-0.186	0.054
Model 2	-0.105(-0.287, 0.077)	-0.112	0.256	-0.142(-0.294, 0.010)	-0.182	0.066
Model 3	-0.101(-0.285, 0.082)	-0.108	0.275	-0.142(-0.290, 0.006)	-0.182	0.059
TyG-index						
Model 1	-1.865(-5.500, 1.771)	-0.095	0.312	-0.010(-3.080, 3.061)	-0.001	0.995
Model 2	-2.354(-6.067, 1.360)	-0.120	0.212	0.197(-2.955, 3.349)	0.012	0.902
Model 3	-2.593(-6.354, 1.168)	-0.132	0.175	-0.203(-3.294, 2.889)	-0.012	0.897
QUICKI						
Model 1	18.317(-78.529, 115.163)	0.037	0.709	73.196(-7.090, 153.481)	0.179	0.074
Model 2	42.718(-61.850, 147.286)	0.087	0.420	74.680(-12.581, 161.940)	0.182	0.093
Model 3	43.356(-61.856, 148.568)	0.088	0.416	76.209(-8.582, 160.999)	0.186	0.078
Hyperinsulinemia						
Model 1	-2.634(-6.925, 1.657)	-0.117	0.226	-3.527(-7.096, 0.043)	-0.188	0.053
Model 2	-3.357(-7.769, 1.055)	-0.149	0.134	-3.466(-7.165, 0.233)	-0.185	0.066
Model 3	-3.651(-8.126, 0.824)	-0.162	0.109	-3.522(-7.153, 0.108)	-0.188	0.057
Insulin resistance						
Model 1	-0.309(-4.660, 4.042)	-0.014	0.888	-4.285(-7.852, -0.717)	-0.227	0.019
Model 2	-1.267(-5.942, 3.408)	-0.056	0.592	-4.485(-8.338, -0.631)	-0.238	0.023
Model 3	-1.549(-6.311, 3.213)	-0.069	0.520	-4.475(-8.270, -0.681)	-0.238	0.021
HOMA-B cell dysfunction						
Model 1	-1.096(-5.710, 3.517)	-0.046	0.639	4.431(0.640, 8.222)	0.222	0.022
Model 2	-0.543(-0.127, 0.330)	0.090	0.380	4.425(0.481, 8.369)	0.222	0.028
Model 3	-0.356(-5.194, 4.481)	-0.015	0.884	4.944(1.115, 8.773)	0.248	0.012

Table 3. Beta coefficients of the association between Insulin-related metabolic indices and PTEN gene expression in adipose tissues. Model 1, adjusted for age. Model 2, adjusted for age and body mass index. Model 3, adjusted for age, body mass index, Kcal intake, and physical activity. Multivariable linear regression analyses (Dependent variables: gene expression) was performed and unstandardized β (95% confidence interval) and standardized (STZ) β were reported. Fasting plasma glucose, Fasting plasma insulin, TyG-index, and QUICKI are continuous numerical variables and hyperinsulinemia, HOMA-IR, and HOMA-B cell dysfunction are binary categorical variables.

method for patient recruitment, which may raise concerns regarding selection bias. Second, the cross-sectional design of our study does not allow for causation to be proven, only for associations between the factors analyzed to be identified. The third key limitation of our study is that the analysis of insulin signaling was based solely on the gene expression levels of PI3K subunits, which may provide an incomplete picture of pathway activity. Since the functional status of the insulin signaling pathway also depends on upstream and downstream genes of this pathway, and post-translational modifications such as phosphorylation and protein-protein interactions, our cross-sectional findings should be interpreted with caution. Nevertheless, these results may serve as a valuable foundation for future experimental studies. Forth, it was not collecting more tissue specimens for matching was impossible due to the study involving human samples. Finally, dietary intake, a significant and modifiable factor in human health, was not assessed as we did not have access to the nutritional information of the individuals. In conclusion, our study found that hyperinsulinemia and IR (measured by HOMA-IR) are directly associated with increased expression of PI3K and Akt, but are inversely related to PTEN, which acts to block the insulin pathway. The PI3K/AKT pathway, working through mTORC1, upregulates the activity of adipogenic transcription factors like PPARγ and C/EBPα. These factors help complete the development of fat cells, leading to more fat storage and less fat breakdown[51,52]. Since extra energy is stored as fat in SAT, it is not unexpected that insulin levels are strongly associated with the expression of PTEN and Akt gene in this tissue.

	Visceral adipose tissue			Subcutaneous adipose tissue		
	β (95% confidence interval)	STZ β	*P* value	β (95% confidence interval)	STZ β	*P* value
Fasting plasma glucose						
Model 1	0.070(-0.106, 0.246)	0.074	0.434	0.044(-0.035, 0.124)	0.104	0.273
Model 2	0.067(-0.113, 0.246)	0.071	0.463	0.042(-0.039, 0.123)	0.099	0.306
Model 3	0.048(-0.137, 0.233)	0.051	0.606	0.030(-0.053, 0.113)	0.070	0.477
Fasting plasma insulin						
Model 1	0.106(-0.157, 0.370)	0.077	0.425	0.040(-0.080, 0.159)	0.064	0.512
Model 2	0.101(-0.169, 0.371)	0.074	0.459	0.035(-0.087, 0.157)	0.056	0.572
Model 3	0.105(-0.166, 0.376)	0.076	0.446	0.036(-0.086, 0.158)	0.058	0.556
TyG-index						
Model 1	3.178(-2.168, 8.524)	0.111	0.241	1.816(-0.601, 4.232)	0.140	0.139
Model 2	3.116(-2.380, 8.612)	0.109	0.264	1.759(-0.726, 4.243)	0.136	0.163
Model 3	2.799(-2.768, 8.367)	0.098	0.321	1.543(-0.951, 4.037)	0.119	0.223
QUICKI						
Model 1	-124.614(-265.383, 16.154)	-0.173	0.082	-47.015(-111.165, 17.135)	-0.144	0.149
Model 2	-134.554(-287.478, 18.371)	-0.187	0.084	-47.428(-117.153, 22.297)	-0.146	0.180
Model 3	-133.305(-286.811, 20.201)	-0.185	0.088	-46.556(-115.850, 22.738)	-0.143	0.186
Hyperinsulinemia						
Model 1	8.550(2.396, 14.704)	0.259	0.007	2.250(-0.605, 5.105)	0.151	0.121
Model 2	8.803(2.429, 15.178)	0.267	0.007	2.196(-0.763, 5.154)	0.147	0.144
Model 3	8.802(2.338, 15.265)	0.267	0.008	2.181(-0.788, 5.150)	0.146	0.148
Insulin resistance						
Model 1	7.033(0.763, 13.303)	0.213	0.028	1.706(-1.184, 4.596)	0.114	0.245
Model 2	7.649(0.883, 14.416)	0.231	0.027	1.647(-1.475, 4.769)	0.110	0.298
Model 3	7.710(0.831, 14.589)	0.233	0.028	1.677(-1.465, 4.819)	0.112	0.292
HOMA-B cell dysfunction						
Model 1	-6.038(-12.743, 0.666)	-0.172	0.077	-0.486(-3.570, 2.598)	-0.031	0.756
Model 2	-6.139(-13.114, 0.835)	-0.175	0.084	-0.295(-3.501, 2.911)	-0.019	0.856
Model 3	-5.806(-12.852, 1.240)	-0.166	0.105	-0.023(-3.225, 3.180)	-0.001	0.989

Table 4. Beta coefficients of the association between Insulin-related metabolic indices and PI3k gene expression in adipose tissues. Model 1, adjusted for age. Model 2, adjusted for age and body mass index. Model 3, adjusted for age, body mass index, Kcal intake, and physical activity. Multivariable linear regression analyses (Dependent variables: gene expression) were performed and unstandardized β (95% confidence interval) and standardized (STZ) β were reported. Fasting plasma glucose, Fasting plasma insulin, TyG-index, and QUICKI are continuous numerical variables and hyperinsulinemia, HOMA-IR, and HOMA-B cell dysfunction are binary categorical variables.

	Visceral adipose tissue			Subcutaneous adipose tissue		
	β (95% confidence interval)	STZ β	*P* value	β (95% confidence interval)	STZ β	*P* value
Fasting plasma glucose						
Model 1	0.019(-0.102, 0.139)	0.029	0.757	0.003(-0.086, 0.092)	0.006	0.947
Model 2	0.015(-0.107, 0.138)	0.024	0.803	-0.006(-0.095, 0.084)	-0.012	0.902
Model 3	0.012(-0.114, 0.139)	0.019	0.846	-0.021(-0.110, 0.067)	-0.045	0.633
Fasting plasma insulin						
Model 1	0.119(-0.060, 0.298)	0.128	0.190	0.142(0.012, 0.273)	0.205	0.033
Model 2	0.116(-0.067, 0.299)	0.125	0.211	0.131(-0.002, 0.264)	0.189	0.053
Model 3	0.121(-0.062, 0.305)	0.130	0.193	0.128(0.001, 0.256)	0.185	0.048
TyG-index						
Model 1	1.712(-1.941, 5.366)	0.088	0.355	0.181(-2.526, 2.888)	0.012	0.895
Model 2	1.627(-2.130, 5.383)	0.083	0.393	-0.181(-2.947, 2.584)	-0.013	0.897
Model 3	1.602(-2.197, 5.401)	0.082	0.405	-0.458(-3.124, 2.208)	-0.032	0.734
QUICKI						
Model 1	-93.867(-189.569, 1.834)	-0.192	0.054	-72.539(-143.066, -2.013)	-0.199	0.044
Model 2	-100.989(-204.949, 2.971)	-0.206	0.057	-65.199(-141.769, 11.372)	-0.179	0.094
Model 3	-100.989(-205.260, 3.281)	-0.206	0.058	-64.053(-137.254, 9.147)	-0.176	0.086
Hyperinsulinemia						
Model 1	6.666(2.514, 10.819)	0.298	0.002	4.118(1.011, 7.225)	0.247	0.010
Model 2	6.862(2.561, 11.163)	0.306	0.002	3.868(0.655, 7.082)	0.232	0.019
Model 3	6.684(2.316, 11.053)	0.298	0.003	4.201(1.118, 7.284)	0.252	0.008
Insulin resistance						
Model 1	5.135(0.873, 9.397)	0.228	0.019	2.985(-0.192, 6.161)	0.178	0.065
Model 2	5.559(0.959, 10.158)	0.247	0.018	2.609(-0.817, 6.035)	0.156	0.134
Model 3	5.296(0.610, 9.982)	0.236	0.027	3.091(-0.211, 6.394)	0.185	0.066
HOMA-B cell dysfunction						
Model 1	-4.515(-9.074, 0.043)	-0.189	0.052	-2.003(-5.405, 1.399)	-0.113	0.246
Model 2	-4.578(-9.321, 0.164)	-0.192	0.058	-1.562(-5.087, 1.963)	-0.088	0.382
Model 3	-4.624(-9.404, 0.156)	-0.194	0.058	-1.211(-4.605, 2.183)	-0.068	0.481

Table 5. Beta coefficients of the association between Insulin-related metabolic indices and Akt gene expression in adipose tissues. Model 1, adjusted for age. Model 2, adjusted for age and body mass index. Model 3, adjusted for age, body mass index, Kcal intake, and physical activity. Multivariable linear regression analyses (Dependent variables: gene expression) was performed and unstandardized β (95% confidence interval) and standardized (STZ) β were reported. Fasting plasma glucose, Fasting plasma insulin, TyG-index, and QUICKI are continuous numerical variables and hyperinsulinemia, HOMA-IR, and HOMA-B cell dysfunction are binary categorical variables.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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References

1. Li, M. et al. Trends in insulin resistance: insights into mechanisms and therapeutic strategy. *Signal. Transduct. Target. Therapy*. **7** (1), 216 (2022).
2. Freeman, A. M., Acevedo, L. A., Pennings, N. & Insulin Resistance StatPearls. Treasure Island FL ineligible companies. Disclosure: Luis Acevedo declares no relevant financial relationships with ineligible companies. Disclosure: Nicholas pennings declares no relevant financial relationships with ineligible companies.: © 2023, StatPearls Publishing LLC.; (2023).
3. Jaquet, D. et al. Combined effects of genetic and environmental factors on insulin resistance associated with reduced fetal growth. *Diabetes* **51** (12), 3473–3478 (2002).
4. Parks, B. W. et al. Genetic architecture of insulin resistance in the mouse. *Cell Metabol.* **21** (2), 334–347 (2015).
5. Gastaldelli, A., Gaggini, M. & DeFronzo, R. A. Role of adipose tissue insulin resistance in the natural history of type 2 diabetes: results from the San Antonio metabolism study. *Diabetes* **66** (4), 815–822 (2017).
6. Virtanen, K. A. et al. Glucose uptake and perfusion in subcutaneous and visceral adipose tissue during insulin stimulation in Nonobese and obese humans. *J. Clin. Endocrinol. Metabolism*. **87** (8), 3902–3910 (2002).
7. Christen, T. et al. Increased glucose uptake in visceral versus subcutaneous adipose tissue revealed by PET imaging. *JACC: Cardiovasc. Imaging*. **3** (8), 843–851 (2010).
8. Coelho, M., Oliveira, T. & Fernandes, R. State of the Art paper biochemistry of adipose tissue: an endocrine organ. *Archives Med. Sci.* **9** (2), 191–200 (2013).

9. Ibrahim, M. M. Subcutaneous and visceral adipose tissue: structural and functional differences. *Obes. Rev.* **11** (1), 11–18 (2010).
10. Khalid, M., Alkaabi, J., Khan, M. A. & Adem, A. Insulin signal transduction perturbations in insulin resistance. *Int. J. Mol. Sci.* **22** (16), 8590 (2021).
11. Xie, Y. et al. PI3K/Akt signaling transduction pathway, erythropoiesis and Glycolysis in hypoxia. *Mol. Med. Rep.* **19** (2), 783–791 (2019).
12. Huang, X., Liu, G., Guo, J. & Su, Z. The PI3K/AKT pathway in obesity and type 2 diabetes. *Int. J. Biol. Sci.* **14** (11), 1483 (2018).
13. Li, A., Qiu, M., Zhou, H., Wang, T. & Guo, W. PTEN, insulin resistance and Cancer. *Curr. Pharm. Design.* **23** (25), 3667–3676 (2017).
14. Haddadi, N. et al. PTEN/PTENP1:'Regulating the regulator of RTK-dependent PI3K/Akt signalling', new targets for cancer therapy. *Mol. Cancer.* **17** (1), 1–14 (2018).
15. Huang, W., Queen, N. J., McMurphy, T. B., Ali, S. & Cao, L. Adipose PTEN regulates adult adipose tissue homeostasis and redistribution via a PTEN-leptin-sympathetic loop. *Mol. Metabolism.* **30**, 48–60 (2019).
16. Kirstein, A. S. et al. PTEN regulates adipose progenitor cell growth, differentiation, and replicative aging. *J. Biol. Chem.* **297** (2), 100968 (2021).
17. Xu, G. et al. MiR-26b modulates insulin sensitivity in adipocytes by interrupting the PTEN/PI3K/AKT pathway. *Int. J. Obes.* **39** (10), 1523–1530 (2015).
18. Pal, A. et al. PTEN mutations as a cause of constitutive insulin sensitivity and obesity. *N. Engl. J. Med.* **367** (11), 1002–1011 (2012).
19. Yuzbashian, E. et al. Determinants of vitamin D receptor gene expression in visceral and subcutaneous adipose tissue in non-obese, obese, and morbidly obese subjects. *J. Steroid Biochem. Mol. Biol.* **187**, 82–87 (2019).
20. Yuzbashian, E. et al. Elevated miR-143 and miR-34a gene expression in human visceral adipose tissue are associated with insulin resistance in non-diabetic adults: a cross-sectional study. *Eat. Weight Disorders: EWD.* **27** (8), 3419–3428 (2022).
21. Committee, I. R. *Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ)-short and long Forms* (http://www ipaq ki se/scoring pdf, 2005).
22. Vasheghani-Farahani, A. et al. The persian, last 7-day, long form of the international physical activity questionnaire: translation and validation study. *Asian J. Sports Med.* **2** (2), 106 (2011).
23. Asghari, G. et al. Reliability, comparative validity and stability of dietary patterns derived from an FFQ in the Tehran lipid and glucose study. *Br. J. Nutr.* **108** (6), 1109–1117 (2012).
24. Brouwer-Brolsma, E. M. et al. The glycaemic index-food-frequency questionnaire: development and validation of a food frequency questionnaire designed to estimate the dietary intake of glycaemic index and glycaemic load: an effort by the PREVIEW consortium. *Nutrients* **11** (1), 13 (2018).
25. Rio, D. C., Ares, M., Hannon, G. J. & Nilsen, T. W. Purification of RNA using TRIzol (TRI reagent). Cold Spring Harbor Protocols. ;2010(6):pdb. prot5439. (2010).
26. Ebrahimi, R., Bahiraee, A., Alipour, N. J., Toolabi, K. & Emamgholipour, S. Evaluation of the housekeeping genes; β-Actin, Glyceraldehyde-3-Phosphate-Dehydrogenase, and 18S rRNA for normalization in Real-Time polymerase chain reaction analysis of gene expression in human adipose tissue. *Archives Med. Lab. Sci.* ;**4**(3). (2018).
27. Kadkhoda, G. et al. Association of dietary intake of fruit and green vegetables with PTEN and P53 mRNA gene expression in visceral and subcutaneous adipose tissues of obese and non-obese adults. *Gene* **733**, 144353 (2020).
28. Montazeri, M. et al. Association of physical activity with increased PI3K and Akt mRNA levels in adipose tissues of obese and non-obese adults. *Sci. Rep.* **13** (1), 9291 (2023).
29. Razavi, S. A. et al. New evidence on tumor suppressor activity of PTEN and KLLN in papillary thyroid carcinoma. *Pathology-Research Pract.* **225**, 153586 (2021).
30. Livak, K. J. & Schmittgen, T. D. Analysis of relative gene expression data using real-time quantitative PCR and the 2− ΔΔCT method. *Methods* **25** (4), 402–408 (2001).
31. Bustin, S. A. et al. *The MIQE Guidelines: M Inimum I Nformation for Publication of Q Uantitative Real-Time PCR E Xperiments* (Oxford University Press, 2009).
32. Ghasemi, A. et al. Cut-off points of homeostasis model assessment of insulin resistance, beta-cell function, and fasting serum insulin to identify future type 2 diabetes: Tehran lipid and glucose study. *Acta Diabetol.* **52**, 905–915 (2015).
33. Muniyappa, R., Lee, S., Chen, H. & Quon, M. J. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. *Am. J. Physiology-Endocrinology Metabolism.* **294** (1), E15–E26 (2008).
34. Song, Y. et al. Insulin sensitivity and insulin secretion determined by homeostasis model assessment and risk of diabetes in a multiethnic cohort of women: the women's health initiative observational study. *Diabetes Care.* **30** (7), 1747–1752 (2007).
35. Niemczyk, S. et al. Homeostatic model assessment indices in evaluation of insulin resistance and secretion in Hemodialysis patients. *Med. Sci. Monitor: Int. Med. J. Experimental Clin. Res.* **19**, 592 (2013).
36. Katz, A. et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J. Clin. Endocrinol. Metabolism.* **85** (7), 2402–2410 (2000).
37. Guerrero-Romero, F. et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *J. Clin. Endocrinol. Metabolism.* **95** (7), 3347–3351 (2010).
38. Zeraatkar, D. et al. Methods for the selection of covariates in nutritional epidemiology studies: A Meta-Epidemiological review. *Curr. Developments Nutr.* **3** (10), nzz104 (2019).
39. Ponkilainen, V. et al. Multivariable models in orthopaedic research: a methodological review of covariate selection and causal relationships. *Osteoarthr. Cartil.* **29** (7), 939–945 (2021).
40. Savova, M. S., Mihaylova, L. V., Tews, D., Wabitsch, M. & Georgiev, M. I. Targeting PI3K/AKT signaling pathway in obesity. *Biomed. Pharmacother.* **159**, 114244 (2023).
41. Fan, W. et al. FOXO1 transrepresses peroxisome proliferator-activated receptor gamma transactivation, coordinating an insulin-induced feed-forward response in adipocytes. *J. Biol. Chem.* **284** (18), 12188–12197 (2009).
42. Teresi, R. E. & Waite, K. A. PPARgamma, PTEN, and the fight against Cancer. *PPAR Res.* **2008**, 932632 (2008).
43. Daneshafrooz, A. et al. The relation of omentin gene expression and glucose homeostasis of visceral and subcutaneous adipose tissues in non-diabetic adults. *Mol. Biol. Rep.* **49** (1), 163–169 (2022).
44. Yang, R. Z. et al. Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. *Am. J. Physiol. Endocrinol. Metab.* **290** (6), E1253–E1261 (2006).
45. Wu, S. S. et al. Omentin-1 stimulates human osteoblast proliferation through PI3K/Akt signal pathway. *Int. J. Endocrinol.* **2013**, 368970 (2013).
46. Chagas, C. L. et al. Different factors modulate visceral and subcutaneous fat accumulation in adults: a single-center study in Brazil. *Front. Nutr.* **12**, 1524389 (2025).
47. Sachdeva, M. M., Stoffers, D. A. & Minireview Meeting the demand for insulin: molecular mechanisms of adaptive postnatal beta-cell mass expansion. *Mol. Endocrinol. (Baltimore Md).* **23** (6), 747–758 (2009).
48. Khin, P. P., Lee, J. H. & Jun, H-S. Pancreatic beta-cell dysfunction in type 2 diabetes. *Eur. J. Inflamm.* **21**, 1721727X231154152 (2023).
49. Wen, X. et al. Signaling pathways in obesity: mechanisms and therapeutic interventions. *Signal. Transduct. Target. Therapy.* **7** (1), 298 (2022).
50. Ahmed, B., Sultana, R. & Greene, M. W. Adipose tissue and insulin resistance in obese. *Biomed. Pharmacother.* **137**, 111315 (2021).

51. Nagai, S., Matsumoto, C., Shibano, M. & Fujimori, K. Suppression of fatty acid and triglyceride synthesis by the flavonoid orientin through decrease of C/EBPδ expression and Inhibition of PI3K/Akt-FOXO1 signaling in adipocytes. *Nutrients* ;**10**(2). (2018).
52. Homan, E. P. et al. Differential roles of FOXO transcription factors on insulin action in brown and white adipose tissue. *J. Clin. Investig.* ;**131**(19). (2021).

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Author contributions
MZ, AZ-V, RS, and HA designed and drafted the manuscript, collected the references, and carried out the primary literature search. FT, MA, GA, MM, AGH, EY, MH, and AKH modify the manuscript and participated in discussions. All authors read and approved the final manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
The Ethics Committee of the Research Institute approved this research for Endocrine Sciences (RIES) of Shahid Beheshti University of Medical Sciences (IR.SBMU.ENDOCRINE.REC.1403.039).

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