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The association between fat distribution and α1-acid glycoprotein levels among adult females in the United States

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Abstract

Background Visceral fat accumulation and obesity-induced chronic inflammation have been proposed as early markers for multiple disease states, especially in women. Nevertheless, the potential impact of fat distribution on α1-acid glycoprotein(AGP), a marker of inflammation, remains unclear. This research was conducted to investigate the relationships among obesity, fat distribution, and AGP levels.

Methods A cross-sectional observational study was performed using blood samples from adult females recruited through the National Health and Nutrition Examination Survey from 2015 to 2018. Serum levels of AGP were measured using the Tina-quant α-1-Acid Glycoprotein Gen.2 assay. Based on the fat distribution data obtained from dual-energy X-ray absorptiometry assessments, body mass index (BMI), total percent fat (TPF), android percent fat (APF), gynoid percent fat (GPF), android fat/gynoid fat ratio (AGR), visceral percent fat (VPF), subcutaneous percent fat (SPF), visceral fat/subcutaneous fat ratio (VSR) were used as dependent variables. To investigate the link between fat distribution and AGP, multivariate linear regression analysis was utilized. Furthermore, a sensitivity analysis was also performed.

Results The present study included 2,295 participants. After adjusting for covariates, BMI, TPF, APF, GPF, VPF, and SPF were found to be positively correlated with AGP levels (BMI: β = 23.65 95%CI:20.90–26.40; TPF: β = 25.91 95%CI:23.02–28.80; APF: β = 25.21 95%CI:22.49–27.93; GPF: β = 19.65 95%CI:16.96–22.34; VPF: β = 12.49 95%CI:9.08–15.90; SPF: β = 5.69, 95%CI:2.89–8.49; AGR: β = 21.14 95%CI:18.16–24.12; VSR: β = 9.35 95%CI:6.11–12.59, all $P < 0.0001$). All the above indicators exhibited a positive dose–response relationship with AGP. In terms of fat distribution, both AGR and VSR showed positive associations with AGP (P for trend < 0.0001). In particular, when compared to individuals in tertile 1 of AGR, participants in tertiles 2 and 3 had 13.42 mg/dL (95% CI 10.66–16.18) and 21.14 mg/dL (95% CI 18.16–24.12) higher AGP levels, respectively. Participants in the highest tertile of VSR were more likely to exhibit a 9.35 mg/dL increase in AGP compared to those in the lowest tertile (95% CI 6.11–12.59).

Conclusions Overall, this study revealed a positive dose-dependent relationship between fat proportion/distribution and AGP levels in women. These findings suggest that physicians can associate abnormal serum AGP and obesity with allow timely interventions.

Keywords α1-acid glycoprotein, Obesity, Fat distribution, Inflammation

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Introduction

In the United States, 38% of adult women are obese [1]. Obesity, once believed to be just a metabolic abnormality, has been shown to demonstrate mutual causality with non-specific immune responses [2–7]. As a result of obesity, women are more vulnerable to fertility issues in addition to metabolic problems including type 2 diabetes and heart disease [8]. Furthermore, the importance of fat distribution is gaining more attention. Accumulation of fat in the abdominal region is linked to health issues related to obesity and even all-cause mortality [9–11]. Conversely, fat tissue gathering in the lower body (gluteofemoral region) has been linked to protective lipid and glucose profiles, along with a decreased risk of cardiovascular and metabolic diseases in population studies [12, 13]. Understanding the full picture of the correlation between body status and fat distribution is vital for health maintenance. In addition, fat distribution is not uniform between men and women. Men and postmenopausal women often exhibit android obesity [14, 15]. This body habitus is also known as an apple-shaped body, due to increased fat in the trunk while the limbs tend to be thin. Women of childbearing age usually demonstrate a gynoid shape [16]. In other words, their bodies tend to have a pear shape due to enhanced fat deposition in the hip and thighs. Differences between these forms of fat distribution are also related to disease predisposition. Excess fat accumulation in the android region is believed to be linked with a higher likelihood of developing cardiovascular disease, hypertension, hyperlipidemia, insulin resistance, and type 2 diabetes [17], whereas gynoid fat accumulation is linked to a lower likelihood of developing metabolic and cardiovascular conditions [18]. In pre-menopausal women altered fat distribution is crucial since android fat accumulation is correlated with a raised prevalence of female infertility [19].

Systemic and tissue-specific chronic inflammation is a common characteristic of obesity [20]. Many findings have suggested that the chronic inflammation caused by fat accumulation differs according to tissue type and distribution. Lim et al. noted that visceral fat in specific tissues released unique inflammatory mediators [21],while Marial et al. suggested that higher fatty deposits in the trunk and inflammation were positively correlated [22]. In women, the release of IL-6 from gluteal and femoral adipose tissue is significantly lower than that from abdominal subcutaneous fat [23]. Therefore, fat distribution strongly correlates with inflammation, with gynoid fat demonstrating a more beneficial inflammatory profile compared to android fat.

α-1-acid glycoprotein (AGP) is a protein that is produced throughout the body in response to inflammation in the liver and peripheral tissues [24].High levels of AGP are often, frequently indicative of adverse conditions. For example, they can lead to tumor-related immunosuppression [25].However, studies have reported methods to inhibit AGP production. For instance, exercise and some drugs can inhibit AGP production [26–28]. In addition, a good dietary pattern will change the glycosylation of AGP. This change was pointed out to be potentially beneficial [29]. Elevated levels of AGP can be observed in inflammatory patients [30, 31], which have also been reported to be a good indicator of inflammation in patients with polycystic ovary syndrome (PCOS), especially those with infertility [32]. Studies One study, having reported on the association between obesity and AGP, found that the association was stronger in women [33]. Indeed, Prioreschi *et al.* also demonstrated that fat accumulation was positively associated with AGP levels in South African women [34], further noting [20] that both the trunk/limb ratio and android/ gynoid ratio were positively associated with AGP. What's more, AGP plays a crucial role in metabolic dysfunction-associated steatotic liver disease (MASLD) which is a well-known inflammation related disease. Studies have shown AGP2 (i.e., ORM2) by activating AMP to effectively hinder adipogenesis which may be a potential target for the treatment of MASLD [35]. Li *et* al. used pharmacological administration of recombinant AGP2 protein to ameliorate hepatocyte injury and degeneration in mice of MASLD, indicating a complex interaction between AGP and liver health dynamics [36]. More evidence is needed to prove the relationship between AGP and fat distribution, especially in larger populations, to better clarify the association among obesity, fat distribution and inflammatory states. The association between AGP in blood and fat distribution is explained in this study for the first time using data gathered from the National Health and Nutrition Examination Survey (NHANES).

To examine the correlation between obesity and fat distribution in NHANES female participants using dual-energy X-ray absorptiometry (DXA) scans is the objective of this research, which aims to provide worthwhile insights into the health consequences of fat distribution on inflammation and related issues in a wider population.

Methods

Participant selection

Initiated in 1999, the NHANES is an ongoing initiative that evaluates people's nutritional status and general health throughout the United States. Orchestrated by the Centers for Disease Control and Prevention (CDC), this comprehensive survey combines detailed interviews with thorough physical assessments (For more details: http://www.cdc.gov/nchs/nhanes.htm). The interview portion probes into various domains such as demographics,

socioeconomic factors, dietary habits, and health-related concerns. Meanwhile, the examination component encompasses a wide range of evaluations including medical and dental check-ups, physiological measurements, and extensive laboratory analyses, all carried out by trained healthcare professionals. The National Center for Health Statistics' Ethics Review Board (Protocol #2011–17 continuation) granted approval for all involved procedures, ensuring that every participant provided written consent prior to participation.

In this study, because AGP data were only available for NHANES survey cycles 2015–2016 and 2017–2018, these cycles were selected. Only women aged 18 to 49 years were included for analysis which encompassed 19,225 participants.

Missing data on AGP; body mass index (BMI); or fat distribution (android percent fat [APF], gynoid percent fat [GPF], visceral adipose tissue mass [VF] and subcutaneous fat [SF]) were excluded. Finally, a total of 2295 participants were included.

Ethical considerations

Each participant gave written consent prior to participation, in accordance with the procedure approved by the Research Ethics Review Board of the National Center for Health Statistics [37]. The NHANES is committed to maintaining strict confidentiality standards and has robust measures in place to safeguard participant anonymity. Given that the current research involved secondary analysis of de-identified data, and that the NHANES dataset is publicly accessible [38], there was no necessity for an institutional review board review for this study [37].

Measurement of AGP

The assessment of AGP was conducted using the Tina-quant α-1-Acid Glycoprotein Gen.2 assay, which operates on the immunological agglutination principle. This process involves the formation of an antigen/antibody complex when anti-AGP antibodies interact with antigens present in the test specimen. This complex leads to agglutination, the intensity of which is quantified turbidimetrically (Refer to: AAGP2 Tina-quant α1-Acid Glycoprotein Gen.2 [package insert]. Indianapolis, IN. Roche Diagnostics. 2014–11, V 9.0.). Each testing sequence included serum quality control (QC) pools from Roche or were generated internally to guarantee accuracy, and was processed in duplicate. These QC samples were then assessed against predefined standards using a robust multi-rule quality control scheme [39]. Data acquisition occurred after the completion of all laboratory analyses. The research team accessed the NHANES database, extracted the pertinent data, and meticulously documented the corresponding measurements.

Measurement of fat distribution

The computation of BMI (kg/m2) involved dividing the individual's weight (in kilograms) by the square of their height (in meters), with the result rounded off to one decimal point. This data collection took place at the Mobile Examination Center (MEC), conducted by skilled health technicians.

As far as body composition analysis goes, DXA is the most widely accepted technique. [40]. Comprehensive DXA scans of the entire body are obtained at the NHANES MEC. When conducting the scanning procedure, the Hologic APEX software is utilized for precise demarcation of the Android and Gynoid (A/G) areas. The bottom trunk section has been specifically labeled as the Android region, with two different lines denoting its borders: a lower line aligning with the pelvic horizontal cut and an upper line automatically positioned above this cut line by the software. The Gynoid region was determined with respect to the Android region's height. The maximum boundary of the Gynoid region is established as 1.5-times the height of the Android region beneath the pelvic line. Conversely, the lower bound of the Gynoid area is set at a distance ensuring the vertical span between the two Gynoid lines is exactly double the height of Android region. The Hologic program carefully placed these demarcating lines to ensure precision and consistency in delineating these essential anatomical regions [41]. The mass of visceral adipose tissue within the abdomen was measured at the approximate level between the L4 and L5 vertebrae. The mass of subcutaneous adipose tissue outside the abdomen was also measured at the approximate level between the L4 and L5 vertebrae. The records of total percent fat (TPF, %), android percent fat (APF, %), and gynoid percent fat (GPF, %) were obtained from NHANES. According to the data for total fat (g), android fat mass (g), subcutaneous fat mass (g), visceral adipose tissue mass (g), and subcutaneous fat mass (g), android fat/gynoid fat ratio (AGR, %), visceral fat/total fat (VPF, %), subcutaneous fat/total fat (SPF, %), visceral fat/subcutaneous fat ratio (VSR, %) were calculated.

Covariates

The study recorded demographic variables such as age, race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Race), education (Less than High School, High School or GED General Educational Development, Above High School), marital status (Live Alone, Living with a Partner) and the income-to-poverty ratio. Biochemical parameters included serum albumin (g/dL), total cholesterol (mg/dL), triglycerides (mg/dL), and energy intake (kcal). The questionnaire-based variables encompassed disease states such as hypertension or not, high cholesterol level

or not, diabetes or not, and lifestyle factors such as physical activity (Vigorous, Moderate, Less Than Moderate) and smoking status.

Data analyses

The analysis followed the recommendation of NHANES on the complex sampling design and weights.

Descriptive statistics were employed for data representation, with continuous variables typically represented by the weighted median and standard deviation (SD), while categorical variables were often depicted using weighted frequency(percentage). The Student 2-tailed t-test or Mann–Whitney U test is utilized to test continuous variables, while the chi-square or Fisher exact test is utilized to test categorical variables.

Applying a multivariate linear regression model to explore the fat distribution's connection with AGP, including an unadjusted model (non-adjusted); a minimally adjusted model (adjust I; adjusted only for age, race, education, marital status, and income-to-poverty ratio); and a fully adjusted model (adjust II; adjusted for age, race, education, marital status, and income: poverty ratio, smoking status, hypertension or not, high cholesterol level or not, diabetes or not and serum albumin, total cholesterol, triglycerides) [42–44]. Calculate β and its 95% confidence intervals (95%CI) to represent the estimated effect value. The tertile of exposure was utilized as an ordinal categorical variable (first to third, with the first tertile set as the reference value) to examine potential trends in this relationship.

To account for missing covariate data, multiple imputation was employed using the R MI procedure, which involved five replications and a chained equation approach. [45, 46], to perform sensitivity analyses (n = 3015).

Data analysis was conducted using R (version 4.3.0; The R Foundation) and Empower (X&Y Solutions Inc) software [47]. The distinction is considered statistically significant at $p < 0.05$.

Results

Population characteristics

Among those recruited, only 2295 female participants successfully passed all screenings (Fig. 1). The characteristics of participants classified by AGP are reported in Table 1(line 482). These included average age, average AGP level, BMI, total percent fat, android percent fat, gynoid percent fat, AGR, subcutaneous percent fat, visceral percent fat, VSR, total cholesterol, triglycerides, C-reactive protein, and albumin.

The present study confirmed the findings that AGP levels are higher corresponding with higher age and higher BMI. BMI was categorized into three ranges for statistical analysis, and the results showed that BMI > 30 (obese group) had the highest AGP levels (percentage 64.41%). Similarly, fat distribution indicators showed the same trend (all $P < 0.05$). Experimental results provided clear support that higher BMI and fat mass are associated with higher AGP levels.

Moreover, higher levels of total cholesterol, triglycerides and lower albumin were observed in this population. AGP levels were higher in smokers compared to non-smokers. More detailed data can be found in Table 1.

Multivariate regression analysis

Table 2 demonstrates the correlation between AGP level and fat distribution through the utilization of multivariable linear regression analysis. BMI, TPF, APF, GPF,

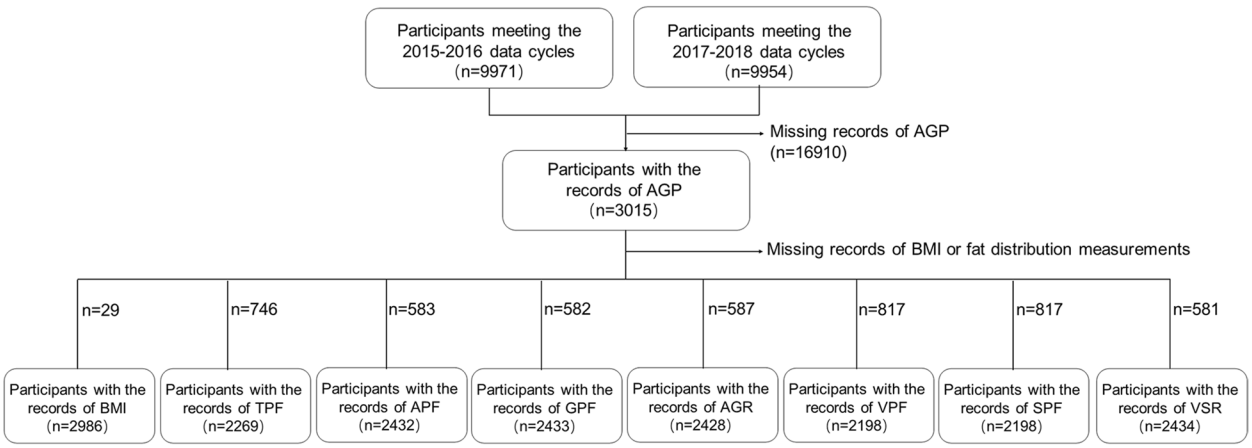

Fig. 1 Flowchart outlining the eligibility and disqualification criteria for female American adults participating in the 2015-2016 and 2017-2018 NHANES of the United States. Abbreviations: AGP: α1 acid glycoprotein; BMI: Body Mass Index; TPF: Total Percent Fat (%); APF: Android percent fat (%); GPF: Gynoid percent fat (%); AGR: Android/Gynoid ratio (%); VPF: Visceral percent fat (%); SPF: Subcutaneous percent fat (%); VSR: Visceral/Subcutaneous ratio (%)

Table 1 Study population characteristics categorized by α1 acid glycoprotein (AGP)

Variables	Total ($n=2295$)	AGP (mg/dL)			*P* Value
		Low ($n=1004$)	Middle ($n=1002$)	High ($n=1009$)	
AGP (mg/dL), Mean ± SD	77.73 ± 24.05	53.13 ± 8.87	75.21 ± 5.73	104.71 ± 16.74	< 0.001
Age (year), Mean ± SD	28.84 ± 11.40	27.39 ± 10.85	29.20 ± 11.49	30.71 ± 11.43	< 0.001
BMI (kg/m^2), n (%)					-
< 25	1274 (32.85%)	547 (55.36%)	319 (32.29%)	122 (12.35%)	
25–30	1309 (33.75%)	280 (28.06%)	412 (41.28%)	306 (30.66%)	
> 30	1295 (33.39%)	128 (12.80%)	298 (29.80%)	574 (57.40%)	
TPF (%), Mean ± SD	37.32 ± 6.81	32.87 ± 5.80	37.96 ± 5.74	41.54 ± 5.61	< 0.001
APF (%), Mean ± SD	37.26 ± 8.70	31.78 ± 7.61	37.84 ± 7.54	42.47 ± 6.96	< 0.001
GPF (%), Mean ± SD	41.19 ± 5.52	38.26 ± 5.19	41.68 ± 4.77	43.80 ± 4.83	< 0.001
AGR (%), Mean ± SD	41.11 ± 13.51	34.56 ± 10.80	41.45 ± 12.85	48.31 ± 13.57	< 0.001
SPF (%), Mean ± SD	6.38 ± 0.87	6.22 ± 0.87	6.44 ± 0.89	6.51 ± 0.81	< 0.001
VPF (%), Mean ± SD	1.26 ± 0.53	1.11 ± 0.47	1.27 ± 0.53	1.44 ± 0.55	< 0.001
VSR (%), Mean ± SD	19.62 ± 8.19	17.75 ± 6.98	19.78 ± 8.10	22.15 ± 9.20	< 0.001
Total Cholesterol(mg/dL), Mean ± SD	177.88 ± 37.16	176.45 ± 38.61	176.72 ± 34.75	180.90 ± 38.35	0.012
Triglycerides (mg/dL), Mean ± SD	110.90 ± 75.05	95.63 ± 67.33	112.19 ± 76.93	128.05 ± 76.16	< 0.001
Albumin (g/dL), Mean ± SD	4.15 ± 0.38	4.20 ± 0.41	4.18 ± 0.35	4.07 ± 0.34	< 0.001
Energy intake (kcal), Mean ± SD	1880.80 ± 832.88	1951.37 ± 819.37	1873.27 ± 798.85	1845.20 ± 817.27	0.014
ratio of family income to poverty (%), Mean ± SD	2.28 ± 1.59	2.56 ± 1.65	2.27 ± 1.56	2.08 ± 1.51	< 0.001
Smoke, n (%)					-
Yes	783 (26.06%)	154 (20.18%)	197 (25.99%)	306 (37.55%)	
No	2222 (73.94%)	609 (79.82%)	561 (74.01%)	509 (62.45%)	
Hypertension, n (%)					-
Yes	456 (13.71%)	67 (7.90%)	115 (13.50%)	168 (18.69%)	
No	2869 (86.29%)	781 (92.10%)	737 (86.50%)	731 (81.31%)	
High cholesterol level, n (%)					-
Yes	413 (12.42%)	94 (11.08%)	109 (12.79%)	140 (15.59%)	
No	2912 (87.58%)	754 (88.92%)	743 (87.21%)	758 (84.41%)	
Diabetes, n (%)					-
Yes	151 (3.90%)	18 (1.81%)	44 (4.46%)	61 (6.17%)	
No	3718 (96.10%)	974 (98.19%)	943 (95.54%)	927 (93.83%)	
Physical Activity, n (%)					-
Vigorous	561 (16.15%)	124 (13.93%)	154 (17.68%)	173 (18.89%)	
Moderate	869 (25.02%)	231 (25.96%)	214 (24.57%)	248 (27.07%)	
Less than moderate	2043 (58.83%)	535 (60.11%)	503 (57.75%)	495 (54.04%)	
Education, n (%)					-
Less than high school	1427 (36.41%)	360 (35.93%)	385 (38.50%)	330 (32.74%)	
High school or GED General educational development	667 (17.02%)	144 (14.37%)	166 (16.60%)	202 (20.04%)	
Above high school	1825 (46.57%)	498 (49.70%)	449 (44.90%)	476 (47.22%)	
Marital status, n (%)					-
Married or living with partner	2116 (63.26%)	560 (66.83%)	514 (60.97%)	548 (61.57%)	
Living alone	1229 (36.74%)	278 (33.17%)	329 (39.03%)	342 (38.43%)	

Table 1 (continued)

Variables	Total ($n=2295$)	AGP (mg/dL)			*P* Value
		Low ($n=1004$)	Middle ($n=1002$)	High ($n=1009$)	
Race, n (%)					-
Mexican American	722 (18.39%)	170 (16.93%)	226 (22.55%)	197 (19.52%)	
Other Hispanic	427 (10.87%)	94 (9.36%)	136 (13.57%)	95 (9.42%)	
Non-Hispanic White	1125 (28.65%)	299 (29.78%)	270 (26.95%)	373 (36.97%)	
Non-Hispanic Black	912 (23.22%)	186 (18.53%)	203 (20.26%)	225 (22.30%)	
Other Race	741 (18.87%)	255 (25.40%)	167 (16.67%)	119 (11.79%)	

The Student 2-tailed t-test or Mann–Whitney U test is utilized to test continuous variables, while chi-square or Fisher exact test is utilized to test categorical variables

The findings demonstrate a statistically significant difference with a P-value of less than 0.05

Abbreviations: AGP: α1 acid glycoprotein; BMI: body mass index; TPF: total percent fat (%); APF: Android percent fat (%); GPF: gynpid percent fat (%); AGR: android/gynoid ratio (%); VPF: visceral percent fat (%); SPF: subcutaneous percent fat (%); VSR: visceral/subcutaneous ratio (%)

AGR, VPF, SPF and VSR showed positive correlations with AGP level (all P values < 0.0001) after adjusting for all covariates (BMI: β = 1.31, 95%CI: 1.18–1.45; TPF: β = 1.72, 95%CI: 1.55–1.89; APF: β = 1.30, 95%CI: 1.17–1.43; GPF: β = 1.59, 95%CI: 1.39–1.79; AGR: β = 0.62, 95%CI: 0.53–0.71; VPF: β = 8.58, 95%CI: 5.90–11.25; SPF: β = 2.79, 95%CI: 1.48–4.11; VSR: β = 0.41, 95%CI: 0.26–0.57; all P values < 0.0001). When all the exposures were divided into three quantiles, pronounced dose–response relationships between BMI, TPF, APF, GPF, AGR, VPF, SPF, VSR and AGP levels were observed.

Further analysis revealed a significant correlation: AGP's effect size were observed to be more pronounced in individuals within the second and third quartiles of BMI compared to those in the first quartile ($P < 0.0001$). This indicates a positive correlation, implying that as AGP level rises, so does the BMI index. Similarly significant positive dose–response relationships were found for both TPF and body fat percent (APF, GPF, VPF, SPF), with quartiles 2 and 3 having meaningfully higher AGP levels than those of quartile 1.

As mentioned above, there was a concentration response relationship between AGR or VSR and AGP. The second and third quantiles of AGR experienced an increase in AGP compared to the first quantile (quantile 2: β = 13.42, 95%CI: 10.66–16.18, $P < 0.0001$; quantile 3: β = 21.14, 95%CI: 18.16–24.12, $P < 0.0001$), while the third quantile of VSR also showed an increase in AGP (quantile 3: β = 9.35, 95%CI: 6.11–12.59, $P < 0.0001$).

Similar to analysis results, the link between AGP and BMI, TPF, APF, GPF, AGR, VPF, SPF, VSR was further confirmed in smooth curve fitting in Fig. 2 which is positive and monotonic. It suggested that the increase in the ratio of android fat to gynoid fat was accompanied by increasing AGP accumulation. In the same vein, the increased ratio of visceral fat to subcutaneous fat was accompanied by an increase AGP accumulation.

In sensitivity analysis, the association between AGP and BMI, TPF, APF, GPF, AGR, VPF, SPF, VSR remained robust after the inclusion of participants missing confounders by multiple imputation (Supplemental Table 1).

Discussion

In this study, increased BMI and excess fat accumulation were meaningfully connected with increased α1-acid glycoprotein concentrations in adult females after full adjustment for covariates. Furthermore, in terms of fat distribution, APF, GPF, VPF, and SPF were found to be positively associated with AGP levels. To investigate the influence of different fat distributions on AGP, the android/gynoid ratio and visceral/subcutaneous ratio were taken as research objects and found to show an increasing trend.

There is a multifactorial and singular effect relationship between obesity, inflammation, and chronic disease [2–7]. During chronic inflammation, inflammatory cells such as neutrophils and monocytes infiltrate adipose tissue [48]. Additionally, enlarged adipocytes are more likely to enter a stressed state and release chemokines such as TNF-α and IL-6, which mediate immune cell infiltration [49].Given that gynoid fat distribution is a protective factor in females, it is relatively less likely to cause inflammation. AGP, an abundant human plasma glycoprotein, is an inflammatory marker, whose serum levels can reach up to 5 times during inflammatory events [50]. A different angle on the relationship between obesity and inflammation is provided by the findings, which showed that fat was associated with an increase in AGP.. Consistent with the results, studies have indicated that higher levels

Table 2 Association between fat distribution and AGP level among American adult female from the National Health and Nutrition Examination Survey 2015–2018

Exposure	Non-adjusted		Adjust I[a]		Adjust II[b]	
	β (95%CI)	*P* value	β (95%CI)	*P* value	β (95%CI)	*P* value
BMI (kg/m2)**						
Continuous	1.43 (1.33, 1.52)	< 0.0001	1.37 (1.26, 1.48)	< 0.0001	1.31 (1.18, 1.45)	< 0.0001
Tertile:						
13.8–23.6	ref		ref		ref	
23.7–30.5	11.97 (10.09, 13.85)	< 0.0001	11.31 (9.09, 13.53)	< 0.0001	9.55 (6.93, 12.17)	< 0.0001
30.6–72.6	26.47 (24.57, 28.36)	< 0.0001	25.75 (23.47, 28.04)	< 0.0001	23.65 (20.90, 26.40)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001
TPF (%)						
Continuous	1.88 (1.75, 2.00)	< 0.0001	1.93 (1.78, 2.07)	< 0.0001	1.72 (1.55, 1.89)	< 0.0001
Tertile:						
15 – 34.4	ref		ref		ref	
34.5 – 40.8	14.40 (12.33, 16.47)	< 0.0001	15.41 (12.99, 17.83)	< 0.0001	13.15 (10.38, 15.92)	< 0.0001
40.9—56.1	28.80 (26.73, 30.87)	< 0.0001	29.43 (26.97, 31.89)	< 0.0001	25.91 (23.02, 28.80)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001
APF (%)						
Continuous	1.43 (1.34, 1.53)	< 0.0001	1.47 (1.37, 1.58)	< 0.0001	1.30 (1.17, 1.43)	< 0.0001
Tertile:						
11.9—33.8	ref		ref		ref	
33.9 – 42	13.47 (11.46, 15.48)	< 0.0001	14.84 (12.50, 17.18)	< 0.0001	12.70 (10.05, 15.36)	< 0.0001
42.1—58.8	28.39 (26.38, 30.40)	< 0.0001	28.98 (26.65, 31.31)	< 0.0001	25.21 (22.49, 27.93)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001
GPF (%)						
Continuous	1.82 (1.66, 1.98)	< 0.0001	1.78 (1.60, 1.96)	< 0.0001	1.59 (1.39, 1.79)	< 0.0001
Tertile:						
16.6 – 39	ref		ref		ref	
39.1 – 43.8	12.22 (10.10, 14.34)	< 0.0001	12.83 (10.42, 15.25)	< 0.0001	10.91 (8.25, 13.58)	< 0.0001
43.9—61.9	23.07 (20.94, 25.19)	< 0.0001	22.50 (20.05, 24.94)	< 0.0001	19.65 (16.96, 22.34)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001
AGR (%)						
Continuous	0.75 (0.69, 0.81)	< 0.0001	0.75 (0.68, 0.82)	< 0.0001	0.62 (0.53, 0.71)	< 0.0001
Tertile:						
15.37 –33.67	ref		ref		ref	
33.68 –45.16	13.34 (11.24, 15.43)	< 0.0001	15.25 (12.82, 17.68)	< 0.0001	13.42 (10.66, 16.18)	< 0.0001
45.17—107.47	24.76 (22.67, 26.86)	< 0.0001	26.10 (23.58, 28.62)	< 0.0001	21.14 (18.16, 24.12)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001
VPF (%)						
Continuous	11.43 (9.65, 13.20)	< 0.0001	12.53 (10.17, 14.89)	< 0.0001	8.58 (5.90, 11.25)	< 0.0001
Tertile:						
0.039 – 0.96	ref		ref		ref	
0.97—1.39	8.00 (5.66, 10.34)	< 0.0001	9.06 (6.28, 11.84)	< 0.0001	7.80 (4.71, 10.89)	< 0.0001
1.40 – 4.22	14.53 (12.21, 16.85)	< 0.0001	16.72 (13.62, 19.82)	< 0.0001	12.49 (9.08, 15.90)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001
SPF (%)						
Continuous	3.74 (2.62, 4.86)	< 0.0001	3.75 (2.51, 4.99)	< 0.0001	2.79 (1.48, 4.11)	< 0.0001
Tertile:						
3.95 – 6.00	ref		ref		ref	
6.01 – 6.75	5.63 (3.25, 8.01)	< 0.0001	6.11 (3.45, 8.77)	< 0.0001	4.89 (2.06, 7.73)	0.0007

Table 2 (continued)

Exposure	Non-adjusted		Adjust I[a]		Adjust II[b]	
	β (95%CI)	*P* value	β (95%CI)	*P* value	β (95%CI)	*P* value
6.76—9.36	7.49 (5.11, 9.87)	< 0.0001	7.80 (5.16, 10.44)	< 0.0001	5.69 (2.89, 8.49)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001
VSR (%)						
Continuous	0.62 (0.51, 0.73)	< 0.0001	0.65 (0.50, 0.79)	< 0.0001	0.41 (0.26, 0.57)	< 0.0001
Tertile:						
0.53 – 15.35	ref		ref		ref	
15.36—21.28	3.22 (0.95, 5.49)	0.0055	3.48 (0.79, 6.17)	0.0113	2.69 (-0.30, 5.67)	0.0777
21.29 – 65.83	11.42 (9.16, 13.67)	< 0.0001	12.18 (9.19, 15.18)	< 0.0001	9.35 (6.11, 12.59)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001

Abbreviations: *AGP* α1 acid glycoprotein, *BMI* Body mass index, *TPF* Total Percent Fat (%), *APF* Android percent fat (%), *GPF* Gynoid percent fat (%), *AGR* Android/Gynoid ratio (%), *VPF* Visceral percent fat (%), *SPF* Subcutaneous percent fat (%), *VSR* Visceral/Subcutaneous ratio (%)

[a] Model I: Adjust for: age; race; education; marital status; ratio of family income to poverty

[b] Model II: Adjust for: age; race; education; marital status; ratio of family income to poverty; physical activity; energy intake(kcal); smoke status; high blood pressure or not; high cholesterol level or not; diabetes or not; albumin (g/dL); total Cholesterol(mg/dL); triglycerides (mg/dL)

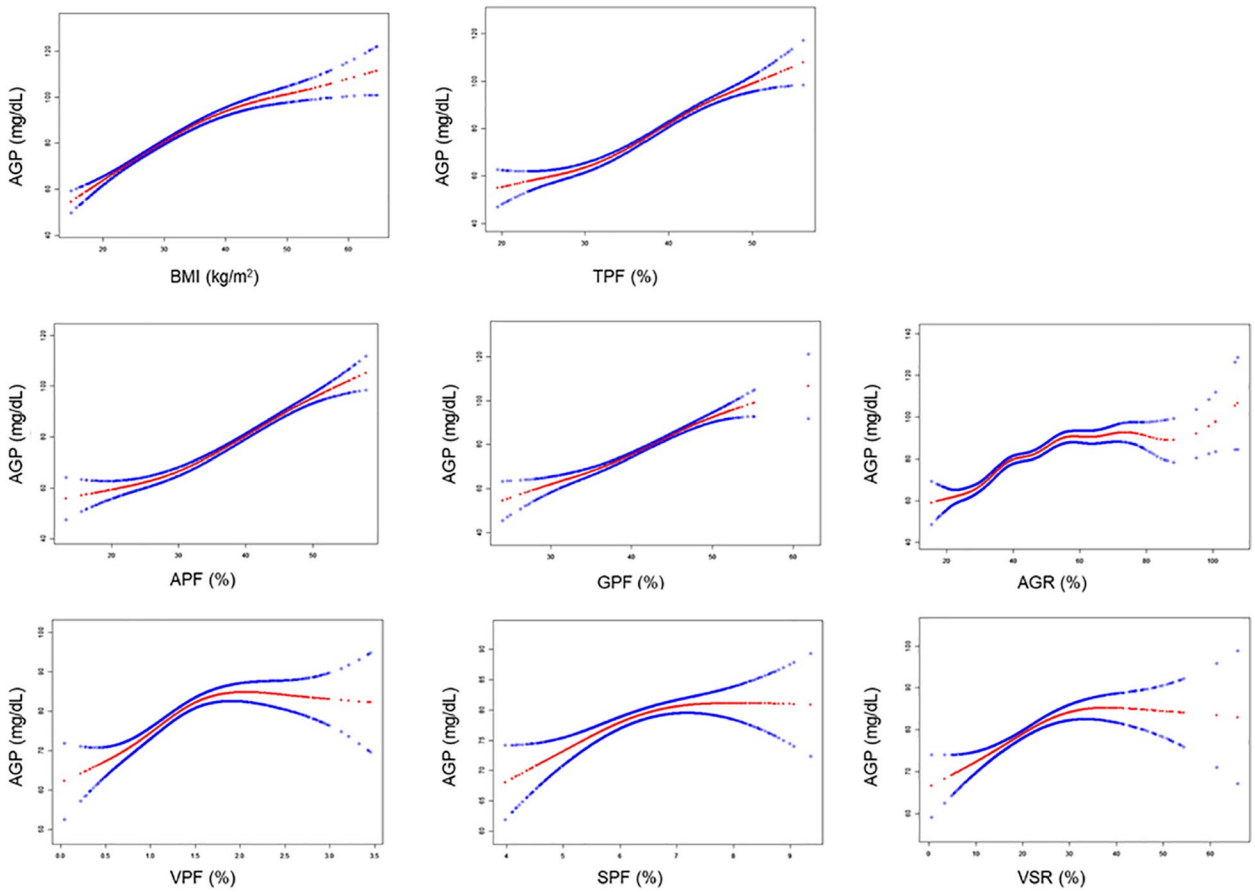

Fig. 2 The red line depicts the fitted smooth curve of the variable, while the space between the two blue lines illustrates the 95% confidence interval (CI)

of inflammatory markers such as IL-6, TNF-α, and leptin are present in the blood of overweight and obese individuals, including adults and children [51]. Furthermore, Palaniswamy *et* al. have argued that an increase in BMI and fat accumulation led to increases in inflammatory markers, including AGP [33]. Significantly, these results support their findings. However as much as we know, this is the first anthropometric study in which the risk of obesity and fat distribution on health is evaluated in a population of only women using AGP levels. The relationship between obesity and AGP has been previously studied with data suggesting that obesity is accompanied by an increase in AGP index [33, 52, 53]. Furthermore, Prioreschi *et* al. emphasized that the accumulation of android fat in South African women is likely the source of an increase in AGP [34];with Black South African women gaining extra fat around their abdomens. The data indicate that the distribution of AGP levels differs according to race. Mexican American and other Hispanic groups had the largest number of people with moderate AGP levels, accounting for 21.18% and 14.74% of the total population, respectively Non-Hispanic Whites accounted for high AGP levels, indicating a greater incidence of obesity among this group. Similarly, the proportion of non-Hispanic Black people with high AGP levels was the largest (22.50%). In contrast, the total number of individuals with low AGP levels was higher in other ethnic groups. One study shown that the prevalence of obesity increased between 2017 and 2018 in both non-Hispanic Whites and non-Hispanic Blacks [54].This data forms the foundation for the viewpoints presented in the research. The variations in obesity levels among ethnic groups may be attributable to differences in sociodemographic status [55].

The present study corroborates findings that the accumulation of visceral and android fat is associated with adverse outcomes and elevated levels of AGP. Consistent with these conclusions, it has been demonstrated that disparities in fat distribution contribute to altered metabolism and an elevated risk of metabolic diseases [56].Android adipocytes tend to increase in size and become more sensitive to lipolytic stimuli. Additionally android fat discharges more lipolysis products into the systemic circulation than gynoid fat. On the contrary, gynoid fat can better retain fatty acids and other lipolysis products, which play a protective role in metabolism [43, 57].Android obesity, also known as abdominal obesity, is harmful to women, since it can lead to abnormal hormone levels [58] and may be related to some forms of female infertility. Abdominal obesity not only causes hypothalamic-pituitary–gonadal axis dysfunction in women with ovulatory dysfunction, but also has toxic effects on reproductive tissue due to excessive fatty acid degradation. This leads to germ cell damage and a chronic low-grade inflammatory state [59–61].Intriguingly, Broughton *et* al. point out that obese women remain infertile even in the absence of ovulatory dysfunction, and it appears that obesity has an effect on the outcome of assisted reproductive technology [62]. As delineated previously, AGP has been identified as an excellent marker of inflammation in patients with PCOS, particularly in those with concurrent infertility. A promising research direction may be the potential association between female infertility and AGP. In short, the results further clarify the association between adiposity, fat distribution and AGP, consistent with previous findings of others groups. This study provides evidence supporting the association between inflammation-related diseases and variations in fat distribution, suggesting that AGP should be considered as a critical indicator of disease in females.

Compared to subcutaneous fat, visceral fat predominantly comprises larger and dysfunctional adipocytes, and is associated with high levels of fatty acid degradation and adipokine secretion leading to inflammation [63–66]. AGP glycoforms are altered during inflammation, thereby positioning AGP as a potential detection index for certain diseases [67].The findings of these experiments indicate that the accumulation of visceral fat correlates with elevated levels of AGP. Previous studies have demonstrated that fatty acids and cytokines released from visceral fat contribute to insulin resistance [68–70].Due to its unique anatomical location, primary hepatic insulin resistance induced by visceral fat may lead to glucose metabolic dysfunction in patients [71].It was hypothesized that higher levels of AGP were related to changes in the cellular environment of the liver. Additionally, females, as a demographic, exhibit variations in visceral fat production. As previously mentioned, women of childbearing age whose estrogen antagonizes the production of visceral fat [14], therefore, visceral obesity is more usual in men and postmenopausal women. Similarly, visceral fat deposition occurs in women with abnormally high androgen levels [72]. Moreover, estrogen itself reduces AGP synthesis [73]. Thus, it was suggested that the accumulation of visceral fat in women of childbearing age may be due to the effects of unbalanced estrogen activity. In summary, a correlation exists between the accrual of visceral adiposity and elevated levels of AGP. In women the detrimental effects of elevated AGP are linked to the endocrine system which will be the focus of future research.

Study strengths and limitations

Although this study used NHANES data to analyze the correlation between fat distribution and the serum AGP levels for the first time, several limitations should be

noted. To begin with, the analysis was conducted only on the adult female population, and the representativeness of the sample needs to be improved. Therefore, whether the findings can be extrapolated to other, larger populations (males, adolescents, and the elderly) needs to be confirmed. Secondly, due to the cross-sectional nature of this study, it is not feasible to definitively determine the causal link between obesity and AGP. There are various reasons for changes in AGP levels, and different conformations of AGP have different physiological functions [74]. It is too simplistic to use AGP as an inflammatory marker and the correlation between obesity and levels of inflammation requires more detailed and diverse indicators. It is worth mentioning that other markers such as C-reactive protein (CRP), adiponectin, inerleukin-6, FGF and TGF [75–79] have been repeatedly reported to have a strong relationship with adiposity and obesity, which also supports this conclusion. Nevertheless, the ability of a single marker to serve as a reliable indicator may be limited. Therefore, developing a combined index of multiple markers as a composite index could represent an innovative approach. Additionally, there are various types of adipose cells, each with its own function and significance [80, 81].To understand the structural and functional aspects of fat cells from different locations, it is essential to conduct animal studies that analyze these cells and their roles at the transcriptome level.

Conclusions

The study established that there is a correlation between fat distribution and AGP levels in adult North American females. Android fat and visceral fat will become our focus in future research. It is essential to prevent the transition to tissue-specific obesity in overweight individuals. It is worth noting that obesity should be considered when abnormal serum AGP levels are detected during physical examinations. Good control of body fat, especially visceral fat, beneficial in improving AGP-related inflammation. Recognizing differences in fat deposition helps to identify obese individuals at risk for inflammation, enabling the implementation of early interventions for those at high risk. The results cast a new light and provide insights into identifying women at risk for poor metabolic health.

Abbreviations

AGP	α1 Acid glycoprotein
AGR	Android fat/gynoid fat ratio
APF	Android percent fat
BMI	Body mass index
CAD	Coronary artery disease
DXA	Dual-energy x-ray absorptiometry
GPF	Gynoid percent fat
MEC	Mobile Examination Center
MASLD	Metabolic dysfunction-associated steatotic liver disease
NHANES	National Health and Nutrition Examination Survey
PCOS	Polycystic ovary syndrome
QC	Quality control
SF	Subcutaneous fat
SPF	Subcutaneous percent fat
TPF	Total percent fat
VPF	Visceral percent fat
VF	Visceral adipose tissue mass
VSR	Visceral fat/subcutaneous fat ratio

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Authors' contributions

Each author contributed to this research work in various ways. The contributions of each author are outlined below: FQ designed the study and performed data screening; TZ conducted bioinformatics analysis of the data; YT and SW were responsible for writing the manuscript and organizing the figures; MW handled manuscript revisions and data verification; DW provided manuscript editing and guidance.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Meldrum DR, Morris MA, Gambone JC. Obesity pandemic: causes, consequences, and solutions—but do we have the will? Fertil Steril. 2017;107(4):833–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0015028217302236. Cited 2024 Jan 23.
2. Monteiro R, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. Mediators of Inflammation. 2010;2010:1–10. Available from: http://www.hindawi.com/journals/mi/2010/289645/. Cited 2024 Jan 12.

3. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–7. Available from: https://www.nature.com/articles/nature05485. Cited 2024 Jan 12.
4. Shoelson SE. Inflammation and insulin resistance. J Clin Invest. 2006;116(7):1793–801. Available from: http://www.jci.org/cgi/doi/10.1172/JCI29069. Cited 2024 Jan 12.
5. Andersen CJ, Murphy KE, Fernandez ML. Impact of obesity and metabolic syndrome on immunity. Adv Nutr. 2016;7(1):66–75. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2161831323001412. Cited 2024 Jan 12.
6. Jiang Z, Wang Y, Zhao X, Cui H, Han M, Ren X, et al. Obesity and chronic kidney disease. Am J Physiol Endocrinol Metab. 2023;324(1):E24-41. Available from: https://journals.physiology.org/doi/10.1152/ajpendo.00179.2022. Cited 2024 Jan 12.
7. Ortega FB, Lavie CJ, Blair SN. Obesity and cardiovascular disease. Circ Res. 2016;118(11):1752–70. Available from: https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.115.306883. Cited 2024 Jan 12.
8. Snider AP, Wood JR. Obesity induces ovarian inflammation and reduces oocyte quality. Reproduction. 2019;158(3):R79-90.
9. Lim S, Meigs JB. Ectopic fat and cardiometabolic and vascular risk. Int J Cardiol. 2013;169(3):166–76.
10. Walker GE, Marzullo P, Ricotti R, Bona G, Prodam F. The pathophysiology of abdominal adipose tissue depots in health and disease. Horm Mol Biol Clin Investig. 2014;19(1):57–74.
11. Yu B, Sun Y, Du X, Zhang H, Chen C, Tan X, et al. Age-specific and sex-specific associations of visceral adipose tissue mass and fat-to-muscle mass ratio with risk of mortality. J Cachexia Sarcopenia Muscle. 2023;14(1):406–17.
12. Goossens GH. The role of adipose tissue dysfunction in the pathogenesis of obesity-related insulin resistance. Physiol Behav. 2008;94(2):206–18.
13. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet. 2005;366(9497):1640–9.
14. Ko SH, Jung Y. Energy metabolism changes and dysregulated lipid metabolism in postmenopausal women. Nutrients. 2021;13(12):4556. Available from: https://www.mdpi.com/2072-6643/13/12/4556. Cited 2024 Jan 12.
15. Palmer BF, Clegg DJ. The sexual dimorphism of obesity. Molecular and Cellular Endocrinology. 2015;402:113–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0303720714004213. Cited 2024 Jan 13.
16. Bjune JI, Strømland PP, Jersin RÅ, Mellgren G, Dankel SN. Metabolic and epigenetic regulation by estrogen in adipocytes. Front Endocrinol. 2022;13:828780. Available from: https://www.frontiersin.org/articles/10.3389/fendo.2022.828780/full. Cited 2024 Jan 13.
17. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, Hong CP, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. Arch Intern Med. 2000;160(14):2117–28.
18. Faulkner JL. Obesity-associated cardiovascular risk in women: hypertension and heart failure. Clin Sci (Lond). 2021;135(12):1523–44.
19. Wang X, Zhu R, Han H, Jin J. Body fat distribution and female infertility: a cross-sectional analysis among US women. Reprod Sci. 2023;30(11):3243–52.
20. Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol Cell Physiol. 2021;320(3):C375–91.
21. Lim S, Meigs JB. Links between ectopic fat and vascular disease in humans. ATVB. 2014;34(9):1820–6. Available from: https://www.ahajournals.org/doi/10.1161/ATVBAHA.114.303035. Cited 2024 Jan 13.
22. Cabral M, Bangdiwala SI, Severo M, Guimarães JT, Nogueira L, Ramos E. Central and peripheral body fat distribution: Different associations with low-grade inflammation in young adults? Nutr Metab Cardiovasc Dis. 2019;29(9):931–8. Available from: https://www.sciencedirect.com/science/article/pii/S0939475319302261. Cited 2023 Nov 30.
23. Pinnick KE, Nicholson G, Manolopoulos KN, McQuaid SE, Valet P, Frayn KN, et al. Distinct developmental profile of lower-body adipose tissue defines resistance against obesity-associated metabolic complications. Diabetes. 2014;63(11):3785–97.
24. Ceciliani F, Lecchi C. The immune functions of α1 acid glycoprotein. CPPS. 2019;20(6):505–24. Available from: http://www.eurekaselect.com/171309/article. Cited 2024 Jan 12.
25. Matsusaka K, Fujiwara Y, Pan C, Esumi S, Saito Y, Bi J, et al. α1-acid glycoprotein enhances the immunosuppressive and protumor functions of tumor-associated macrophages. Cancer Res. 2021;81(17):4545–59. Available from: https://aacrjournals.org/cancerres/article/81/17/4545/670275/1-Acid-Glycoprotein-Enhances-the-Immunosuppressive. Cited 2024 Jul 1.
26. Mejdoubi N, Henriques C, Bui E, Durand G, Lardeux B, Porquet D. Growth hormone inhibits rat liver alpha-1-acid glycoprotein gene expression in vivo and in vitro. Hepatology. 1999;29(1):186–94.
27. Castriota G, Thompson GM, Lin Y, Scherer PE, Moller DE, Berger JP. Peroxisome proliferator-activated receptor gamma agonists inhibit adipocyte expression of alpha1-acid glycoprotein. Cell Biol Int. 2007;31(6):586–91.
28. Tékus É, Váczi M, Horváth-Szalai Z, Ludány A, Kőszegi T, Wilhelm M. Plasma actin, gelsolin and orosomucoid levels after eccentric exercise. J Hum Kinet. 2017;56:99–108.
29. Kim T, Xie Y, Li Q, Artegoitia VM, Lebrilla CB, Keim NL, et al. Diet affects glycosylation of serum proteins in women at risk for cardiometabolic disease. Eur J Nutr. 2021;60(7):3727–41.
30. Duché JC, Urien S, Simon N, Malaurie E, Monnet I, Barré J. Expression of the genetic variants of human alpha-1-acid glycoprotein in cancer. Clinical Biochemistry. 2000;33(3):197–202. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0009912000000485. Cited 2024 Jan 12.
31. Higai K, Azuma Y, Aoki Y, Matsumoto K. Altered glycosylation of α1-acid glycoprotein in patients with inflammation and diabetes mellitus. Clinica Chimica Acta. 2003;329(1–2):117–25. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0009898102004278. Cited 2024 Jan 12.
32. Durmuş M, Uzunlar Ö, Çelik H, Çandar T. Does alpha-1-acid glycoprotein determine for infertility in polycystic ovary syndrome? Eur J Obstet Gynecol Reprod Biol. 2022;274:155–9.
33. Palaniswamy S, Gill D, De Silva NM, Lowry E, Jokelainen J, Karhu T, et al. Could vitamin D reduce obesity-associated inflammation? Observational and Mendelian randomization study. Am J Clin Nutr. 2020;111(5):1036–47.
34. Prioreschi A, Koethe JR, Aronoff DM, Goldstein JA, Norris SA. Relationships between adiposity distribution and metabolic health in preconception women in South Africa. Obes Sci Pract. 2022;8(4):500–9.
35. Levander L, Gunnarsson P, Grenegård M, Rydén I, Påhlsson P. Effects of α1-acid glycoprotein fucosylation on its Ca2+ mobilizing capacity in neutrophils. Scand J Immunol. 2009;69(5):412–20. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1365-3083.2009.02240.x. Cited 2024 Jan 12.
36. Li L, Sun H, Chen J, Ding C, Yang X, Han H, et al. Mitigation of non-alcoholic steatohepatitis via recombinant Orosomucoid 2, an acute phase protein modulating the Erk1/2-PPARγ-Cd36 pathway. Cell Rep. 2023;42(7):112697.
37. NHANES - NCHS Research Ethics Review Board Approval. Available from: https://www.cdc.gov/nchs/nhanes/irba98.htm (2022)
38. NHANES - National Health and Nutrition Examination Survey Homepage. 2023. Available from: https://www.cdc.gov/nchs/nhanes/index.htm. Cited 2023 Nov 4.
39. Caudill SP, Schleicher RL, Pirkle JL. Multi-rule quality control for the age-related eye disease study. Stat Med. 2008;27(20):4094–106.
40. Lu Y, Mathur AK, Blunt BA, Gluer CC, Will AS, Fuerst TP, et al. Dual X-ray absorptiometry quality control: comparison of visual examination and process-control charts. J Bone Miner Res. 1996;11(5):626–37.
41. Shepherd JA, Fan B, Lu Y, Wu XP, Wacker WK, Ergun DL, et al. A multinational study to develop universal standardization of whole-body bone density and composition using GE healthcare Lunar and hologic DXA systems. J Bone Miner Res. 2012;27(10):2208–16.
42. Ramírez Alvarado MM, Sánchez Roitz C, Pérez Díaz A, Millán BE. [Effect of a high saturated fatty acids load on serum concentrations of C-reactive protein, alpha1-antitrypsin, fibrinogen and alpha1-acid glycoprotein in obese women]. Nutr Hosp. 2010;25(1):72–9.
43. Goossens GH. The metabolic phenotype in obesity: fat mass, body fat distribution, and adipose tissue function. Obes Facts. 2017;10(3):207–15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5644968/. Cited 2023 Nov 15.
44. Chen J, Li K, Shao J, Lai Z, Feng Y, Liu B. The Correlation of Apolipoprotein B with Alterations in Specific Fat Depots Content in Adults. Int J Mol Sci. 2023;24(7):6310. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10094599/. Cited 2023 Nov 20.

45. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;29(338):b2393.
46. Park SY, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW. Association of coffee consumption with total and cause-specific mortality among nonwhite populations. Ann Intern Med. 2017;167(4):228–35.
47. 易侕统计 | **生物与流行病学**统计软**件** | EmpowerStats. 2023. Available from: https://www.empowerstats.net/cn/. Cited 2023 Nov 6.
48. Suzuki K. Chronic inflammation as an immunological abnormality and effectiveness of exercise. Biomolecules. 2019;9(6):223. Available from: https://www.mdpi.com/2218-273X/9/6/223. Cited 2024 Jan 12.
49. Batra A, Siegmund B. The role of visceral fat. Dig Dis. 2012;30(1):70–4. Available from: https://www.karger.com/Article/FullText/335722. Cited 2024 Jan 12.
50. Fernandes CL, Ligabue-Braun R, Verli H. Structural glycobiology of human α 1 -acid glycoprotein and its implications for pharmacokinetics and inflammation. Glycobiology. 2015;25(10):1125–33. Available from: https://academic.oup.com/glycob/article-lookup/doi/10.1093/glycob/cwv041. Cited 2024 Jan 12.
51. Das UN. Is obesity an inflammatory condition? Nutrition. 2001;17(11–12):953–66.
52. Ferrari M, Cuenca-García M, Valtueña J, Moreno LA, Censi L, González-Gross M, et al. Inflammation profile in overweight/obese adolescents in Europe: an analysis in relation to iron status. Eur J Clin Nutr. 2015;69(2):247–55.
53. Sobieska M, Gajewska E, Kalmus G, Samborski W. Obesity, physical fitness, and inflammatory markers in Polish children. Med Sci Monit. 2013;24(19):493–500.
54. Liu B, Du Y, Wu Y, Snetselaar LG, Wallace RB, Bao W. Trends in obesity and adiposity measures by race or ethnicity among adults in the United States 2011–18: population based study. BMJ. 2021;16(372):n365.
55. Lincoln KD, Abdou CM, Lloyd D. Race and socioeconomic differences in obesity and depression among Black and non-Hispanic White Americans. J Health Care Poor Underserved. 2014;25(1):257–75.
56. Kissebah AH, Vydelingum N, Murray R, Evans DJ, Kalkhoff RK, Adams PW. Relation of body fat distribution to metabolic complications of obesity*. J Clin Endocrinol Metab. 1982;54(2):254–60. Available from: https://academic.oup.com/jcem/article-lookup/doi/10.1210/jcem-54-2-254. Cited 2024 Jan 12.
57. Björntorp P. Metabolic implications of body fat distribution. Diabetes Care. 1991;14(12):1132–43. Available from: https://diabetesjournals.org/care/article/14/12/1132/16502/Metabolic-Implications-of-Body-Fat-Distribution. Cited 2024 Jan 12.
58. Kirschner MA, Samojlik E, Drejka M, Szmal E, Schneider G, Ertel N. Androgen-estrogen metabolism in women with upper body versus lower body obesity*. J Clin Endocrinol Metab. 1990;70(2):473–9. Available from: https://academic.oup.com/jcem/article-lookup/doi/10.1210/jcem-70-2-473. Cited 2024 Jan 12.
59. Diamanti-Kandarakis E, Bergiele A. The influence of obesity on hyperandrogenism and infertility in the female. Obes Rev. 2001;2(4):231–8. Available from: https://onlinelibrary.wiley.com/doi/10.1046/j.1467-789X.2001.00041.x.
60. Douchi T, Kuwahata R, Yamamoto S, Oki T, Yamasaki H, Nagata Y. Relationship of upper body obesity to menstrual disorders. Acta Obstet Gynecol Scand. 2002;81(2):147–50. Available from: https://obgyn.onlinelibrary.wiley.com/doi/10.1034/j.1600-0412.2002.810210.x.
61. Morán C, Hernández E, Ruíz JE, Fonseca ME, Bermúdez JA, Zárate A. Upper Body Obesity and Hyperinsulinemia Are Associated with Anovulation. Gynecol Obstet Invest. 1999;47(1):1–5. Available from: https://www.karger.com/Article/FullText/10052. Cited 2024 Jan 12.
62. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. Fertil Steril. 2017;107(4):840–7.
63. Mathieu P, Poirier P, Pibarot P, Lemieux I, Després JP. Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. Hypertension. 2009;53(4):577–84.
64. Neeland IJ, Hughes C, Ayers CR, Malloy CR, Jin ES. Effects of visceral adiposity on glycerol pathways in gluconeogenesis. Metabolism. 2017;67:80–9.
65. Würfel M, Blüher M, Stumvoll M, Ebert T, Kovacs P, Tönjes A, et al. Adipokines as clinically relevant therapeutic targets in obesity. Biomedicines. 2023;11(5): 1427.
66. Kolb H. Obese visceral fat tissue inflammation: from protective to detrimental? BMC Med. 2022;20(1):494.
67. Mackiewicz A, Mackiewicz K. Glycoforms of serum ?1-acid glycoprotein as markers of inflammation and cancer. Glycoconjugate J. 1995;12(3):241–7. Available from: http://link.springer.com/10.1007/BF00731326.
68. Hansen GT, Sobreira DR, Weber ZT, Thornburg AG, Aneas I, Zhang L, et al. Genetics of sexually dimorphic adipose distribution in humans. Nat Genet. 2023;55(3):461–70. Available from: https://www.nature.com/articles/s41588-023-01306-0.
69. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Adams-Huet B, Grundy SM. Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. Diabetes. 1996;45(12):1684–93. Available from: https://diabetesjournals.org/diabetes/article/45/12/1684/9046/Relationship-of-Generalized-and-Regional-Adiposity.
70. Bensussen A, Torres-Magallanes JA, Roces de Álvarez-Buylla E. Molecular tracking of insulin resistance and inflammation development on visceral adipose tissue. Front Immunol. 2023;14: 1014778.
71. Bergman RN, Kim SP, Catalano KJ, Hsu IR, Chiu JD, Kabir M, et al. Why visceral fat is bad: mechanisms of the metabolic syndrome. Obesity. 2006;14(S2). Available from: https://onlinelibrary.wiley.com/doi/10.1038/oby.2006.277. Cited 2024 Jan 12.
72. Elbers JMH, Asscheman H, Seidell JC, Megens JAJ, Gooren LJG. Long-term testosterone administration increases visceral fat in female to male transsexuals1. J Clin Endocrinol Metab. 1997;82(7):2044. Available from: https://academic.oup.com/jcem/article/82/7/2044/2865884. Cited 2024 Jan 12.
73. Tsen LC, Arthur GR, Datta S, Hornstein MD, Bader AM. Estrogen-induced changes in protein binding of bupivacaine during in vitro fertilization. Anesthesiology. 1997;87(4):879–83.
74. Van Dijk W, Brinkman-Van Der Linden ECM, Havenaar EC. Glycosylation of .ALPHA.1-Acid Glycoprotein(Orosomucoid) in health and disease: occurrence, regulation and possible funtional implications. Trends in Glycoscience and Glycotechnology. 1998;10(53):235–45. Available from: http://www.jstage.jst.go.jp/article/tigg1989/10/53/10_53_235/_article/-char/ja/. Cited 2024 Jan 12.
75. Shi C, Zhu L, Chen X, Gu N, Chen L, Zhu L, et al. IL-6 and TNF-α induced obesity-related inflammatory response through transcriptional regulation of miR-146b. J Interferon Cytokine Res. 2014;34(5):342–8. Available from: http://www.liebertpub.com/doi/10.1089/jir.2013.0078.
76. Timpson NJ, Nordestgaard BG, Harbord RM, Zacho J, Frayling TM, Tybjærg-Hansen A, et al. C-reactive protein levels and body mass index: elucidating direction of causation through reciprocal Mendelian randomization. Int J Obes. 2011;35(2):300–8. Available from: https://www.nature.com/articles/ijo2010137.
77. Nigro E, Scudiero O, Monaco ML, Palmieri A, Mazzarella G, Costagliola C, et al. New insight into adiponectin role in obesity and obesity-related diseases. Biomed Res Int. 2014;2014:1–14. Available from: http://www.hindawi.com/journals/bmri/2014/658913/. Cited 2024 Jun 3.
78. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol. 2012;8(8):457–65. Available from: https://www.nature.com/articles/nrendo.2012.49. Cited 2024 Jun 3.
79. Yadav H, Quijano C, Kamaraju AK, Gavrilova O, Malek R, Chen W, et al. Protection from obesity and diabetes by blockade of TGF-β/Smad3 signaling. Cell Metabolism. 2011;14(1):67–79. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1550413111002154. Cited 2024 Jun 3.
80. Cristancho AG, Lazar MA. Forming functional fat: a growing understanding of adipocyte differentiation. Nat Rev Mol Cell Biol. 2011;12(11):722–34. Available from: https://www.nature.com/articles/nrm3198. Cited 2024 Jun 3.
81. Corvera S. Cellular heterogeneity in adipose tissues. Annu Rev Physiol. 2021;83(1):257–78. Available from: https://www.annualreviews.org/doi/10.1146/annurev-physiol-031620-095446. Cited 2024 Jun 3.

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