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META-ANALYSIS

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Correlations Between Abnormal Glucose Metabolism and Bone Mineral Density or Bone Metabolism

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

CD Yang Qu
C Ming-Yang Kang
E Rong-Peng Dong
AB Jian-Wu Zhao

Department of Orthopedics, Second Hospital of Jilin University, Changchun, Jilin, P.R. China

Corresponding Author: Jian-Wu Zhao, e-mail: zhaojianwu831@163.com
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Background: The aim of this meta-analysis was to explore the correlations of abnormal glucose metabolism (AGM) with bone mineral density (BMD) and bone metabolism.

Material/Methods: Relevant studies were identified using computerized and manual search strategies. The included studies were in strict accordance with inclusion and exclusion criteria. Statistical analyses were conducted with the Comprehensive Meta-analysis 2.0 (Biostat Inc., Englewood, NJ, USA).

Results: Our present meta-analysis initially searched 844 studies, and 7 studies were eventually incorporated in the present meta-analysis. These 7 cohort studies included 1123 subjects altogether (560 patients with AGM and 563 healthy controls). The results showed that bone mass index (BMI), insulin, and insulin resistance (IR) of patients with AGM were significantly higher than that of the population with normal glucose metabolism (BMI: SMD=1.658, 95% CI=0.663~2.654, *P*=0.001; insulin: SMD=0.544, 95% CI=0.030~1.058, *P*=0.038; IR: SMD=8.767, 95% CI=4.178~13.356, *P*<0.001). However, the results also indicated there was no obvious difference in osteocalcin (OC) and BMD in patients with AGM and the population with normal glucose metabolism (OC: SMD=0.293, 95% CI=–0.023~0.609, *P*=0.069; BMD: SMD=0.805, 95% CI=–0. 212~1.821, *P*=0.121).

Conclusions: Our meta-analysis results suggest that AGM might lead to increased BMI, insulin, and IR, while it has no significant correlation with BMD or bone metabolism.

MeSH Keywords: Bone Density • Glucose Metabolism Disorders • Insulin • Insulin Resistance • Osteocalcin

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Background

Abnormal glucose metabolism (AGM) is a type of endocrine and metabolic disease that is clinically manifested with high levels of blood sugar maintained for a prolonged period of time [1]. It is currently established that AGM comprises distinct forms of disorders, ranging from impaired glucose regulation (IGR) to diabetes mellitus (DM) [2,3]. Epidemiological data revealed an alarming the number of individuals with AGM, which is expected to increase from the present 190 million to 366 million by 2030 worldwide [4]. In addition, a higher rate of disease occurrence is observed in Asian populations, strongly suggesting the emerging potential of AGM becoming epidemic in developing countries [5]. It is generally believed that the major risk factors for developing AGM lie in the complex interactions between genetic, psychological, and social environments [6,7]. The primary symptoms of AGM are urination frequency, polydipsia, and polyphagia, which are often accompanied by other clinical complications [8–10]. Previous studies have demonstrated that AGM preventable through a variety of strategies, including performing sufficient physical exercise and adopting a healthy diet [11].

Bone mineral density (BMD) is medically defined as the amount of mineral matter per square centimeter of bones, which also acts as an indirect indicator for the risk of developing osteoporosis and fracture in clinical medicine [12]. BMD is clinically featured by its painlessness and non-invasiveness, which involves low radiation exposure frequently performed in nuclear medicine or radiology departments in clinics or hospitals [13,14]. Various risk factors have been identified to be indicative of low BMD, including older age, vertebral abnormalities, primary hyperparathyroidism, history of eating disorders, and other additional factors [15,16]. As a lifelong process, bone metabolism is characterized by generation and substitution of new bone tissues for mature bone tissues within the skeleton [17]. It also controls bone regeneration and replacement following injuries, such as fractures and micro-damage that occur during normal activities [18]. Bone metabolism is maintained at a balanced rate through a complex crosstalk between growth and differentiation that heavily depends upon various regulatory signaling pathways, which includes hormones, cytokines, bone marrow-derived membrane, and growth factors [19–21].

AGM is a disease that includes inflammation (a factor associated with reduced BMD) and obesity (a factor related to increased BMD) [22]. Study reported that the systemic inflammation associated with the metabolic syndrome, such as AGM, may activate bone resorption and further result in reduced BMD [23]. In contrast, Mitsuyo found higher BMD among subjects with AGM, in which obesity appeared to be the main component increasing BMD [24]. However, a definitive role for AGM in BMD and bone metabolism remains to be fully elucidated, as several recent independent studies have reported discordant and seemingly conflicting results [25–28]. Higher BMD was protective in obese individuals with AGM; however, fracture risk was increased in more advanced diabetes, which may change bone quality with BMD remaining unchanged [29,30]. Weight loss is advocated in AGM patients to reduce their cardiovascular risk, but it may also reduce BMD and increase bone turnover [31,32]. AGM has some detrimental impacts on bone metabolism, and it has significant outcomes for patients with diabetes with regard to decreased BMD and increased risk of fractures [33,34]. Therefore, we performed a meta-analysis to evaluate the correlation of AGM with BMD and bone metabolism.

Material and Methods

Data sources and keywords

Research articles that addressed the correlation of AGM with BMD and bone metabolism published before September 1, 2014 were obtained by searching multiple independent computerized databases (PubMed, China BioMedicine (CBM), Embase, Web of Science, China National Knowledge Infrastructure (CNKI) and Cochrane Library), utilizing selected keywords ("glucose tolerance test" or "glucose metabolism") and ("osteoporosis", "OP", "bone metabolism", "bone density", "bone mineral density" or "BMD"). The language of the articles was not restricted. The bibliographies within the papers were further examined manually to identify additional relevant papers.

Study selection

In order to be enrolled in our meta-analysis, published papers must meet the following selection criteria: (1) designed as clinical cohort studies regarding the correlation between AGM and BMD or bone metabolism; (2) studied patients with AGM in comparison with controls that had normal glucose metabolism; (3) had complete data available; and (4) written in Chinese or English. Exclusion criteria were: (1) lack of integrity for the literature data, (2) baseline characteristics being considerably different for the subjects between the observation and control group, and (3) repetition of published documents.

Data extraction

Relevant information from selected articles was extracted by 2 independent investigators and recorded on a predefined form. Specifically, the following data were obtained: first author, time of publication, language, disease, diagnostic criterion, age, gender, study type, country, ethnicity, study design, sample size, and intervention measures.

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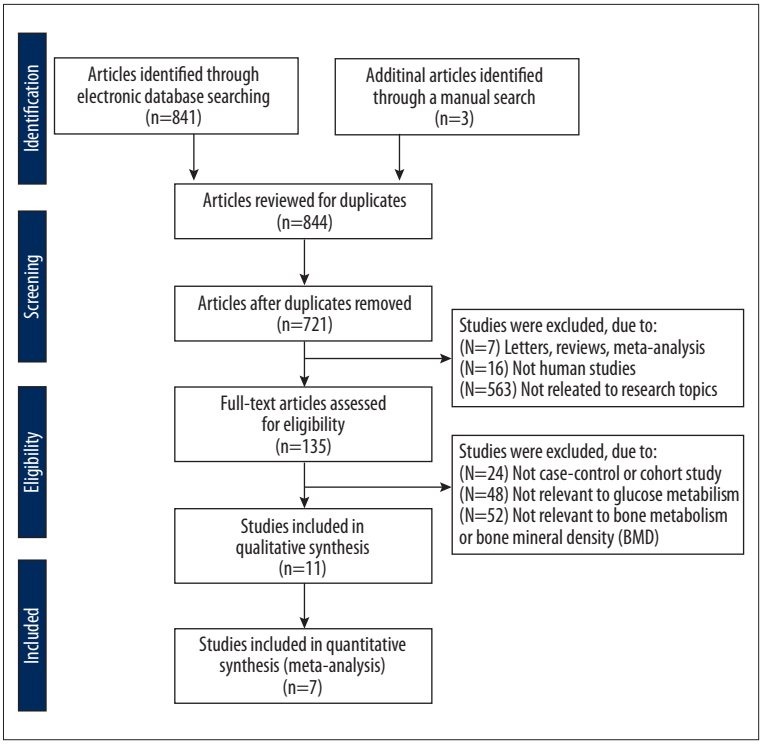

Figure 1. Flow chart showing the study selection procedure based upon the inclusion and exclusion criteria. This ultimately led to 7 studies being included in this meta-analysis.

Quality assessment

The Newcastle-Ottawa Scale (NOS) criteria were utilized to assess the studies independently [35]. The NOS criteria are scored as: (1) group selection: whether the exposed group has adequate or pool representation (NOS01); whether the unexposed group and exposed group come from the same population (NOS02); whether the included studies have reliably recorded and structured interviews (NOS03); whether observational outcomes were described at the beginning of the selected studies(NOS04); (2) group comparability: whether the study selected the most important factors with the controls being appropriately analyzed (NOS05); whether the study controls other important confounding factors (NOS06); (3) group results: whether the study depended upon a blinded method (NOS07); whether the follow-up time was sufficient for the results to be valid (NOS08); whether there are a small number of missing subjects during the follow-up assessment despite no introduced deviation (NOS09); whether the non-response rate is the same in 2 groups (NOS10). Discrepancies for the NOS scores of the included articles were further addressed by a third reviewer by group discussion and consulting.

Statistical analysis

Our meta-analysis was carried out with Comprehensive Meta-analysis 2.0 (Biostat Inc., Englewood, New Jersey, USA). The standard mean difference (SMD) with its 95% confidence interval (95% CI) was utilized for evaluating the differences between the observation and control group. The Z test was performed to determine the significance of the overall effect value. The Cochran's Q-statistic was used for evaluating the heterogeneity across the enrolled studies, which was further measured by I^2 test (0%, no heterogeneity; 100%, maximal heterogeneity). $P<0.05$ was considered statistically significant [36,37]. A random-effects model was employed when heterogeneity was detected among studies, whereas a fixed-effects model was implemented in the presence of acceptable homogeneity [38]. Sensitivity analysis was conducted to assess if the results were affected after exclusion of any single selected study. The funnel plots together with the Egger's linear regression test were constructed to determine if a publication bias was present [39].

Results

Included studies

Figure 1 presented the procedure that led to the identification and inclusion of eligible studies for our analysis. We initially retrieved a total of 844 studies after searching the electronic database combined with manual search. There were 123 duplicates, 16 non-human studies, 7 letters, reviews or meta-analysis, and 563 non-related articles that were considered ineligible and thus excluded. The remaining 135 studies were further reviewed, among which 124 were also excluded because 24 were non-cohort studies, 48 irrelevant to glucose

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Table 1. Main characteristics and methodological quality of all eligible studies.

First author	Year	Ethnicity	Diagnostic criteria	Gender (M/F)		Age (years)		Outcomes
				Case	Control	Case	Control	
Afghani A [45]	2005	Caucasians	NR	26/20	80/58	12.1±1.8	11.8±1.7	BMI, BMD, glucose, insulin, IR
Anastasilakis A [44]	2007	Caucasians	NR	0/23		65.6±1.8		Glucose, insulin, IR
Hu CH [43]	2007	Asians	WHO	38/24	34/31	53.2±9.1	52.4±10.2	BMD, BMI
Rochefort GY [41]	2011	Asians	NR	12/15	NR	9–12	NR	BMI, BMD, insulin, Oc
Yavropoulou MP [40]	2011	Caucasians	NR	39/79	28/50	NR	NR	BMI, blood glucose, Oc
Liu MY [42]	2012	Asians	WHO	155/0		70.6±2.1	69.4±2.4	BMI, BMD
Camhi SM-a [50]	2014	Caucasians	NR	136/0		43.6±11.2	37.8±12.7	BMD, BMI
Camhi SM-b [50]	2014	Caucasians		0/259		43.5±10.1	39.2±10.6	BMD, BMI

M – male; F – female; NR – not report. WHO – World Health Organization; BMI – bone mass index; BMD – bone mineral density; IR – insulin resistance; Oc – osteocalcin.

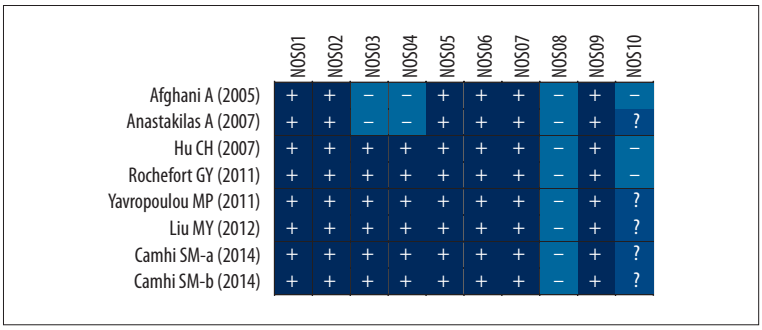

Figure 2. Quality assessment of the included studies by the Newcastle-Ottawa Scale scores.

metabolism and 52 irrelevant to bone metabolism or BMD. Since there were 4 papers among the remaining ones that lacked sufficient information, this eventually led to 7 studies being enrolled for the analysis. These ultimately selected cohort studies, published between 2005 and 2014, evaluated the correlation of AGM with BMD and bone metabolism in Asian and Caucasian populations (each in 3 studies) with a total of 1123 subjects (560 patients with AGM and 563 healthy controls) [40–46]. Among these 7 articles, 2 were performed in the USA, 2 in Greece, 2 in China, and 1 in Israel. Only 2 of these studies were in accordance with the WHO diagnostic criteria. Table 1 and Figure 2 illustrate the baseline characteristics in detail, as well as the NOS quality evaluation for the ultimately selected 7 studies.

Pooled outcome of meta-analysis

The differences with respect to body mass index (BMI), insulin, and insulin resistance (IR) between patients with AGM and healthy controls with normal glucose metabolism were reported in 6, 3, and 2 studies, respectively. Considering the heterogeneity (I^2 >50%, P<0.05) detected in our analysis, a random-effects model was applied to pool the data concerning these 3 indexes. The results demonstrated that BMI, insulin, and IR for patients with AGM were significantly higher than for the control population with normal glucose metabolism (BMI: SMD=1.658, 95% CI=0. 663~2.654, P=0. 001; insulin: SMD=0.544, 95% CI=0.030~1.058, P=0.038; IR: SMD=8.767, 95% CI=4.178~13.356, P<0.001) (Figure 3A–3C). On the other hand, the differences with respect to osteocalcin (OC) and BMD between patients with AGM and the population with normal glucose metabolism were reported in 2 and 5 studies, respectively. Accordingly, a random-effects model was also applied to pool the data of these 2 indexes given the detected heterogeneity ($I2$ > 50%, P < 0.05). However, the results revealed no significant difference concerning the OC and BMD in patients with AGM and the control subjects with normal glucose metabolism (OC: SMD=0.293, 95% CI=-0.023~0.609, P=0.069; BMD: SMD=0.805, 95% CI=–0. 212~1.821, P=0. 121) (Figure 3D, 3E).

Sensitivity analysis and publication bias

Using the sensitivity analysis in our investigation, we revealed that removal of any single included study had a negligible

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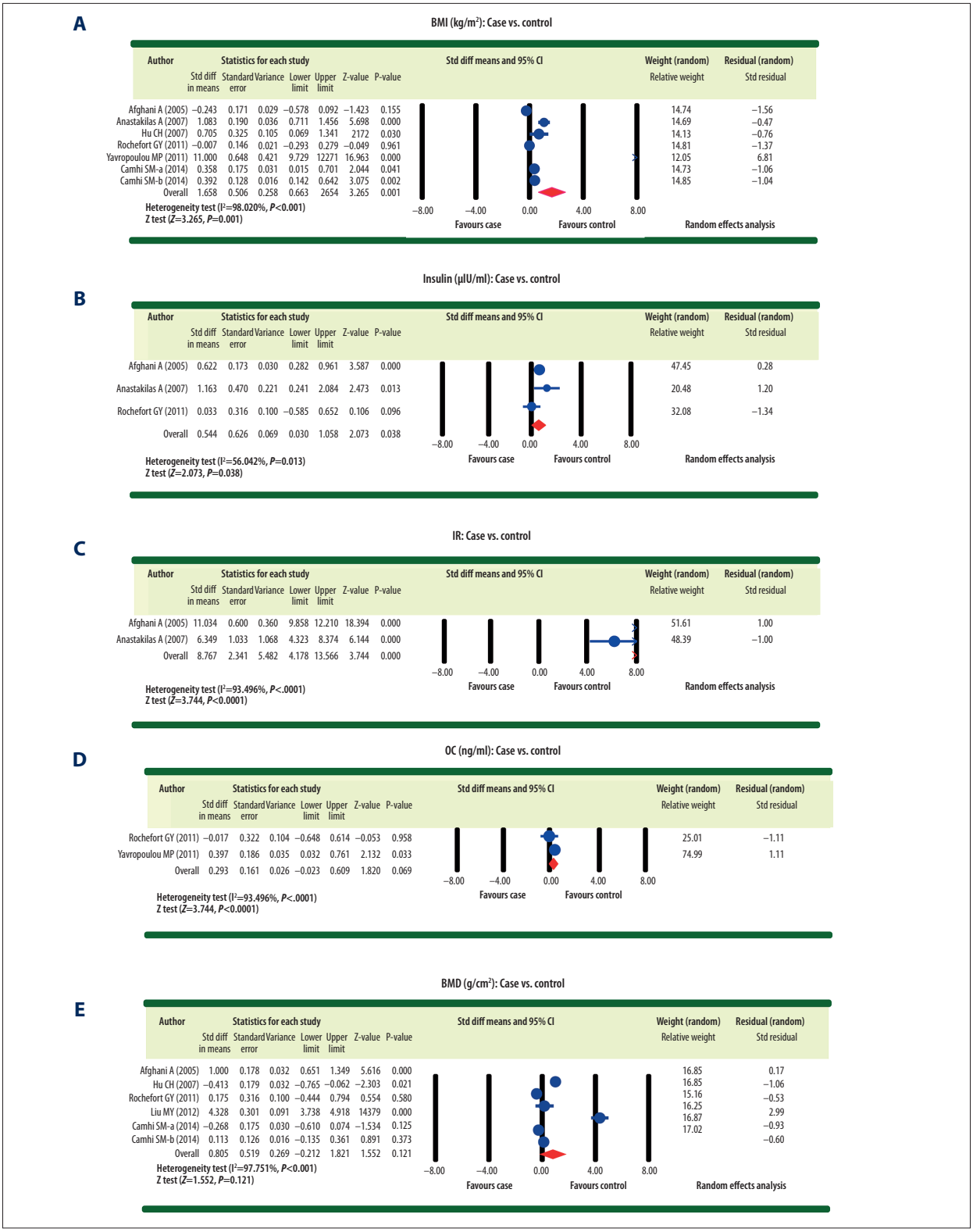

Figure 3. Forest plots illustrating the differences for osteocalcin, bone mineral density, body mass index, insulin, and insulin resistance between patients with abnormal glucose metabolism and healthy controls with normal glucose metabolism ((**A**) Body mass index (case *vs.* control); (**B**) Insulin (case *vs.* control); (**C**) Insulin resistance (case *vs.* control); (**D**) Osteocalcin (case *vs.* control); (**E**) Bone mineral density (case *vs.* control)).

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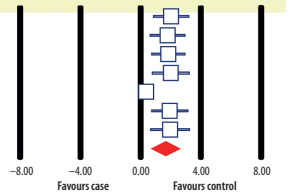
A

BMI (kg/m²): Case vs. control

Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Afghani A (2005)	2.024	0.598	0.357	0.852	3.195	3.385	0.001
Anastakilas A (2007)	1.789	0.589	0.347	0.634	3.944	3.036	0.002
Hu CH (2007)	1.830	0.566	0.320	0.721	2.939	3.234	0.001
Rochefort GY (2011)	2.003	0.627	0.393	0.774	3.232	3.194	0.001
Yavropoulou MP (2011)	0.359	0.185	0.034	−0.003	0.722	1.941	0.052
Camhi SM-a (2014)	1.930	0.612	0.375	0.730	3.130	3.151	0.002
Camhi SM-b (2014)	1.953	0.659	0.434	0.661	3.245	2.963	0.003
Overall	1.658	0.508	0.258	0.663	2.654	3.265	0.001

Statistics with study removed

Std diff in means (95% CI) with study removed



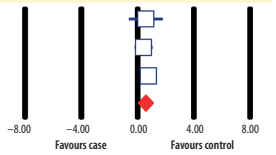
B

Insulin (μIU/ml): Case vs. control

Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Afghani A (2005)	0.544	0.562	0.316	−0.557	1.646	0.968	0.333
Anastakilas A (2007)	0.387	0.288	0.083	−0.178	0.951	1.342	0.180
Rochefort GY (2011)	0.716	0.205	0.042	0.314	1.117	3.494	0.000
Overall	0.544	0.262	0.069	0.030	1.058	2.073	0.038

Statistics with study removed

Std diff in means (95% CI) with study removed



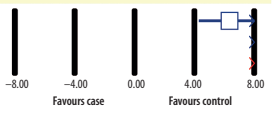
C

IR: Case vs. control

Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Afghani A (2005)	6.349	1.033	1.068	4.323	8.374	6.144	0.000
Anastakilas A (2007)	11.034	0.600	0.360	9.858	12.210	18.394	0.000
Overall	8.767	2.341	5.482	4.178	13.656	3.744	0.000

Statistics with study removed

Std diff in means (95% CI) with study removed



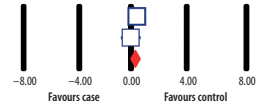
D

OC (ng/ml): Case vs. control

Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Rochefort GY (2011)	0.397	0.186	0.035	0.032	0.761	2.132	0.333
Yavropoulou MP (2011)	−0.017	0.322	0.104	−0.648	0.614	−0.053	0.958
Overall	0.293	0.161	0.026	−0.023	0.609	0.820	0.069

Statistics with study removed

Std diff in means (95% CI) with study removed



E

BMD (g/cm²): Case vs. control

Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Afghani A (2005)	0.769	0.629	0.396	−0.464	2.002	1.223	0.221
Hu CH (2007)	1.054	0.616	0.379	−0.152	2.261	1.712	0.087
Rochefort GY (2011)	0.928	0.592	0.351	−0.232	2.089	1.567	0.117
Liu MY (2012)	0.119	0.249	0.062	−0.370	0.608	0.477	0.633
Camhi SM-a (2014)	1.026	0.630	0.397	−0.210	2.261	1.627	0.104
Camhi SM-b (2014)	0.953	0.700	0.490	−0.420	2.325	1.361	0.174
Overall	0.805	0.519	0.269	−0.212	1.821	1.552	0.121

Statistics with study removed

Std diff in means (95% CI) with study removed

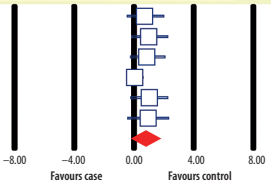


Figure 4. Sensitivity analyses regarding the differences for osteocalcin, bone mineral density, body mass index, insulin, and insulin resistance between patients with abnormal glucose metabolism and healthy controls with normal glucose metabolism ((**A**) Body mass index (case *vs.* control); (**B**) Insulin (case *vs.* control); (**C**) Insulin resistance (case *vs.* control); (**D**) Osteocalcin (case *vs.* control); (**E**) Bone mineral density (case *vs.* control)).

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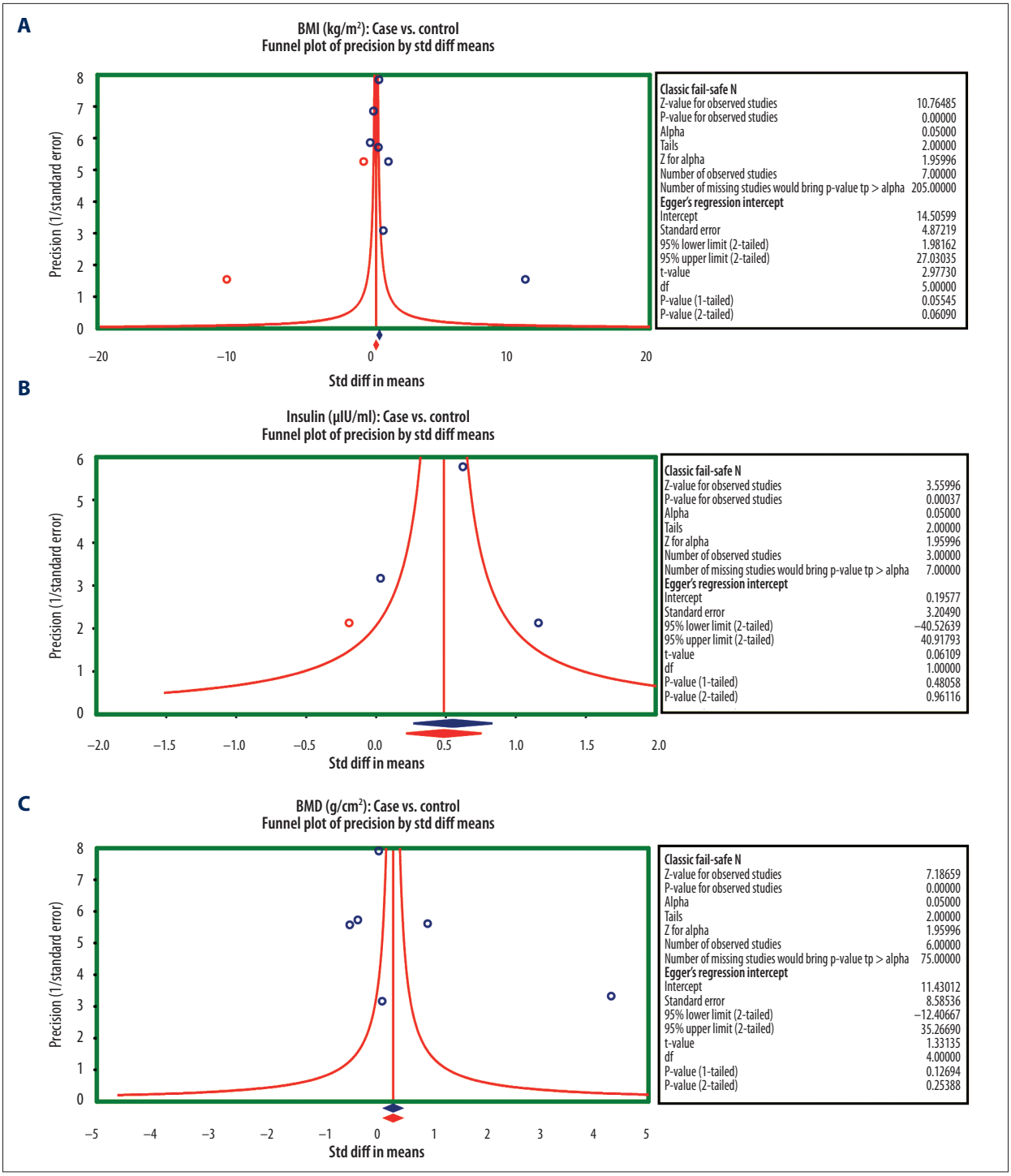

Figure 5. Funnel plots to detect a potential publication bias on the differences for osteocalcin, bone mineral density, body mass index, insulin, and insulin resistance between patients with abnormal glucose metabolism and healthy controls with normal glucose metabolism ((**A**) Body mass index (case *vs.* control); (**B**) Insulin (case *vs.* control); (**C**) Bone mineral density (case *vs.* control)).

impact on our findings, indicating the stability of our analysis. Results from the sensitivity analysis suggested that all included studies had no detected effect on the merging effect value SMD of the correlation between AGM and BMD or bone metabolism (Figure 4A–4E). The symmetrical funnel plots for all 7 studies did not support the presence of a publication bias. This was further corroborated by the Egger linear regression analysis (all $P>0.05$) (Figure 5A–5C).

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Discussion

To definitively explore the correlation of AGM with BMD and bone metabolism, a systematical meta-analysis was performed. Based on the experimental data obtained from previous studies, our meta-analysis revealed that BMI, insulin, and IR for patients with AGM were significantly higher than for healthy individuals with normal glucose metabolism, implying that AGM might lead to increased BMI, insulin, and IR. BMI is frequently utilized as a technically straightforward and easily interpreted method to assess the extent to which an individual's height-corrected body weight deviates from normal [47]. According to the WHO criteria, BMI less than 18.5 is considered as underweight, which indicates potential health problems such as possible malnutrition and eating disorders; in contrast, BMI greater than 25 is considered as overweight, especially for those who may be obese with BMI above 30 [48]. As a peptide hormone secreted by the beta cells in the pancreas, insulin plays an indispensible role in regulating the metabolism of carbohydrates and fats. Mechanistically, insulin exerts it physiological functions by facilitating the absorption of glucose from blood to fat tissues and skeletal muscles and simultaneously promoting fat deposition with suppressed energy consumption [49,50]. Insulin induces a variety of increased (glycogen synthesis, lipid synthesis, amino acid and potassium uptake and esterification of fatty acids) and decreased (proteolysis, lipolysis, gluconeogenesis and autophagy) cellular activities [51,52]. However, there are aberrant conditions when cells are unable to biologically respond to insulin, resulting in metabolic syndromes and DM, which is medically defined as IR [53]. Intriguingly, the physiological consequences of IR seem to be context-dependent. For example, IR in muscle and fat cells compromises glucose uptake, whereas IR in liver cells diminishes synthesis and storage of glycogens and causes failed suppression of production and release of glucose into the blood [54]. In line with this, our meta-analysis postulated that increased BMI, insulin, and IR are closely associated with AGM.

To further explore the correlation between AGM and other indexes, a subgroup meta-analysis was subsequently conducted with more accuracy and rigorousness. The selected indexes included OC and BMD. Interestingly, the stratified analysis indicated that OC was not significantly different between patients with AGM and healthy controls with normal glucose metabolism. Meanwhile, BMD was also not significantly different between patients with AGM and healthy individuals with normal glucose metabolism. Taken together, our findings are in line with previous studies that consistently showed no detectable correlation of AGM with OC and BMD.

Similar to other published meta-analysis, we also acknowledged several limitations in the current meta-analysis. Firstly, our analysis was severely limited by the number of the included studies, which might not accurately and strictly represent a suitable dataset for the statistical analysis. Secondly, the sample size in the enrolled studies was relatively small, which might not provide sufficiently valid data for our results. A third limitation lies in the potential language bias in our selection procedure, since only those studies published in English and Chinese were included. Notably, we identified only 2 eligible studies published in Chinese from those 7 studies. Last but not least, our analysis was restricted by the selection procedure for controls, which was only population-based and might not represent the entire general population.

Conclusions

In summary, our meta-analysis indicates that GM might lead to increased BMI, insulin, and IR. In contrast, it has no significant correlation with BMD or bone metabolism.

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Competing interests

The authors have declared that no competing interests exist.

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