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ORIGINAL ARTICLE

Association between osteocalcin and glucose metabolism: a meta-analysis

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Abstract
Summary This meta-analysis aimed to investigate the associations between osteocalcin (Ocn) and fasting plasma glucose (FPG) and glycated hemoglobin A1c (HbA1c). It was revealed that both total Ocn and undercarboxylated Ocn (unOcn) were negatively related with FPG and HbA1c, and the association of unOcn with FPG was more pronounced in men.
Introduction The aim of this study was to investigate the strength of associations between Ocn and FPG and HbA1c using a meta-analysis approach.
Methods A search was carried out using the databases of PubMed, ISI Web of Science, and the Cochrane library from 2007 to 2014 to identify related studies. A pooled effect size with 95 % confidence intervals (CI) was derived.
Results The meta-analysis included 39 studies involving 23,381 participants. The overall correlation was −0.16 (95 % CI, −0.19 to −0.14) between total Ocn (tOcn) and FPG and −0.15 (95 % CI, −0.20 to −0.11) between undercarboxylated Ocn (unOcn) and FPG. In the analysis of the association between Ocn and HbA1c, the pooled correlation was −0.16 (95 % CI, −0.18 to −0.14) for tOcn and −0.16 (95 % CI, −0.23 to −0.08) for unOcn. The magnitude of the correlation between unOcn and FPG is significantly higher in men than in women (r=−0.18, 95 % CI, −0.21 to −0.14; r=−0.09, 95 % CI, −0. 13 to −0.05, respectively; P for interaction<0.05). Similar trend was also found between unOcn and HbA1c but without significance (for men, r=−0.19, 95 % CI, −0.24 to −0.14; for women, r=−0.09, 95 % CI, −0.22 to 0.04, respectively; P for interaction>0.05). No indication of significant publication bias was found in any method.
Conclusions This meta-analysis demonstrated that both unOcn and tOcn were similarly and negatively correlated with FPG and HbA1c in humans. The negative correlations between unOcn and glucose metabolism appear to be more pronounced in men than in women.

Keywords Fasting plasma glucose · Glycated hemoglobin A1c · Meta-analysis · Osteocalcin

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Introduction

In recent years, the skeleton was believed to play a certain role in regulating whole body glucose homeostasis through endocrine pathways [1]. Accumulating evidence from mice studies has demonstrated that osteocalcin (Ocn), a bone protein synthesized and secreted by osteoblasts, especially in its undercarboxylated form, is generally acknowledged to fulfill this skeleton endocrine function [1]. It was shown that mice lacking *Ocn* ($Ocn^{-/-}$) displayed glucose intolerance due to impaired insulin secretion and insulin resistance [1] while the metabolic phenotypes of mice lacking the gene *Esp*

($Esp^{-/-}$), which had high circulating undercarboxylated Ocn (unOcn) but normal serum levels of total Ocn (tOcn), were just opposite to those observed in $Ocn^{-/-}$ mice [1]. What's more, administration of unOcn to mice significantly improved glucose tolerance and protected both wild-type and high-fat diet mice from obesity and type 2 diabetes [2, 3].

Since the discovery of the hormonal properties of Ocn, many clinical studies have investigated the associations between serum tOcn and/or unOcn and biomarkers of glucose metabolism in humans [4–6]. However, the results are contradictory. Some studies have demonstrated higher serum levels of either tOcn or unOcn were correlated with lower fasting plasma glucose (FPG) or glycated hemoglobin A1c (HbA1c) [5, 7–9], whereas no such associations could be found in other studies [10–13]. It is also not clear in humans whether unOcn is more closely related with glucose-related parameters than tOcn as observed in mice studies. In addition, the study populations in human studies were heterogeneous; some studies were performed in normal adults, some in patients with different degrees of glucose tolerance, including type 2 diabetes, while some others in participants without defining diabetes status [6, 14–16]. The gender, ethnicities, and sample size of these human studies were also varied greatly. All these factors may contribute to the conflicting outcomes. In this circumstance, meta-analysis offers an effective approach to explore the overall estimate between Ocn and glucose metabolism. Therefore, we conducted a meta-analysis of the existing data sources to investigate the magnitude of associations between different subtypes of Ocn (tOcn and unOcn) and FPG or HbA1c. We also tried to give a comprehensive view of these relationships in different populations according to ethnicity and gender.

Methods

Search strategy

We searched PubMed, ISI Web of Knowledge, and the Cochrane library from August 2007 to June 2014 to identify studies that evaluated the association between Ocn and FPG. We used the following keywords: "osteocalcin," "bone Gla protein," or "Bone gamma-carboxyglutamate protein" in combination with "glucose" or "glycated hemoglobin A1c" or "HbA1c" with no restriction. In addition, we read the reference lists of original articles and reviews in case of missing studies that were relevant to our current meta-analysis. The inclusion criteria of the studies were (1) original studies published in English language, investigating associations between Ocn and FPG or HbA1c; (2) observational studies conducted with adults; and (3) studies reporting a correlation coefficient *r*. We excluded review papers, letters, case-reports, studies with children, adolescents or pregnant women, diseases apparently affecting serum Ocn, as well as animal studies. If the same population was used in more than one study, only the study providing more information was included.

Quality assessment and data extraction

Two of the authors (Liu DM and Guo XZ) independently searched all of the related studies and identified eligible studies meeting the above criteria. The quality of the studies was assessed according to the Agency for Healthcare Research and Quality guidelines. Data extracted included the authors, year of publication, ethnicity, age, gender, sample size, and the *r* value between tOcn or unOcn and FPG or HbA1c. When the results were presented from various covariate analyses, we extracted the unadjusted ones because some of the studies over-adjusted for multiple confounders, which may influence the causal pathway between Ocn and glucose metabolism. Discrepancies were resolved upon discussion. We contacted the authors of the primary studies for detailed information when necessary.

The Spearman correlation coefficients were first transformed to Pearson correlation coefficients [17]. A Fisher transformation was used to convert each correlation coefficient into an approximately normal distribution for meta-analysis, and then back-transformed into the original correlation coefficients in the final results [18].

Statistical analysis

A pooled effect size of the included studies was determined using a random-effects model by the method of DerSimonian and Laird [19], and the results were presented as correlation coefficients with 95 % confidence intervals (CI). Analyses of the different populations were conducted according to ethnicity (East Asian and Caucasian) and gender (men and women) using a random-effects model or fixed-effects model to give further insight into the associations between Ocn, FPG and HbA1c in different populations.

The heterogeneity of correlations across the studies was assessed by the Cochran *Q* test, where $P<0.10$ was considered statistically heterogeneous. An additional measure of heterogeneity was tested using the coefficient of inconsistency (I^2) statistic with 25, 50, and 75 % corresponding to cut-off points for low, moderate, and high degrees of heterogeneity, respectively [20, 21]. In addition, we performed subgroup analysis based on ethnicity and gender to investigate potential sources of heterogeneity.

For the sensitivity analysis, we repeated the calculations by omitting one study at one time to assess the stability of the estimates. Furthermore, we used the Begg's adjusted rank correlation test and the Egger's regression asymmetry test to detect publication bias, for both tests, $P>0.05$ represented no significant publication bias [22, 23].

All of the statistical analyses were performed using STATA version 12.0 (Stata Corp, College Station, TX, USA).

Results

Characteristics of studies

Briefly, 1370 references (716 from PubMed, 651 from ISI web of science, and 3 from the Cochrane library) were identified. Of those references, 1287 were excluded due to duplication and on a screening of the abstracts or titles. The full texts of the remaining 83 references were examined in detail, and 44 references were excluded according to the inclusion criteria. Finally, 39 citations involving 23,381 subjects were included in the meta-analysis [4–16, 24–49] (Fig. 1). The *r* values of the 15 studies included in this meta-analysis were transformed from Spearman correlation coefficients.

Thirty-four studies including 19,333 subjects were selected to analyze the association between tOcn and FPG, and 9 studies involving 6294 subjects were obtained to calculate the overall correlation coefficient between unOcn and FPG. Moreover, 21 studies containing 10,363 participants and 7 studies including 6145 participants were selected to analyze the relationships between tOcn or unOcn and HbA1c, respectively. The serum unOcn were all reported as absolute value quantified by electrochemiluminescence immunoassay (ECLIA) [14, 27, 28, 38, 40], or enzyme-linked immunosorbent assay (ELISA) [30, 33, 41, 43, 45]. The detailed information regarding the included studies is shown in Table 1. We included case-control or prospective studies that reported the correlation coefficients between Ocn and FPG or HbA1c at baseline.

Overall analysis and sensitivity analysis

For FPG, a random-effects meta-analysis revealed that the pooled estimate was −0.16 (95 % CI, −0.19 to −0.14) between tOcn and FPG with significant heterogeneity (I^2=66.2 %, P<0.001) (Fig. 2a). The summary correlation between unOcn and FPG was −0.15 (95 % CI, −0.20 to −0.11), and clear heterogeneity was observed (I^2=52.5 %, P=0.017) (Fig. 2b). For HbA1c, a fixed-effects model was used to calculate the correlation coefficient between tOcn and HbA1c (r=−0.16, 95 % CI, −0.18 to −0.14; I^2=43.1 %) (Fig. 3a), whereas a random-effects model was applied to obtain the overall estimate between unOcn and HbA1c (r=−0.16, 95 % CI, −0.23 to −0.08; I^2=84.5 %) (Fig. 3b).

Due to significant heterogeneity, a sensitivity analysis was conducted to investigate the stability of the estimates and explore the potential sources of heterogeneity. No single study displayed a substantial influence on the summary effect size

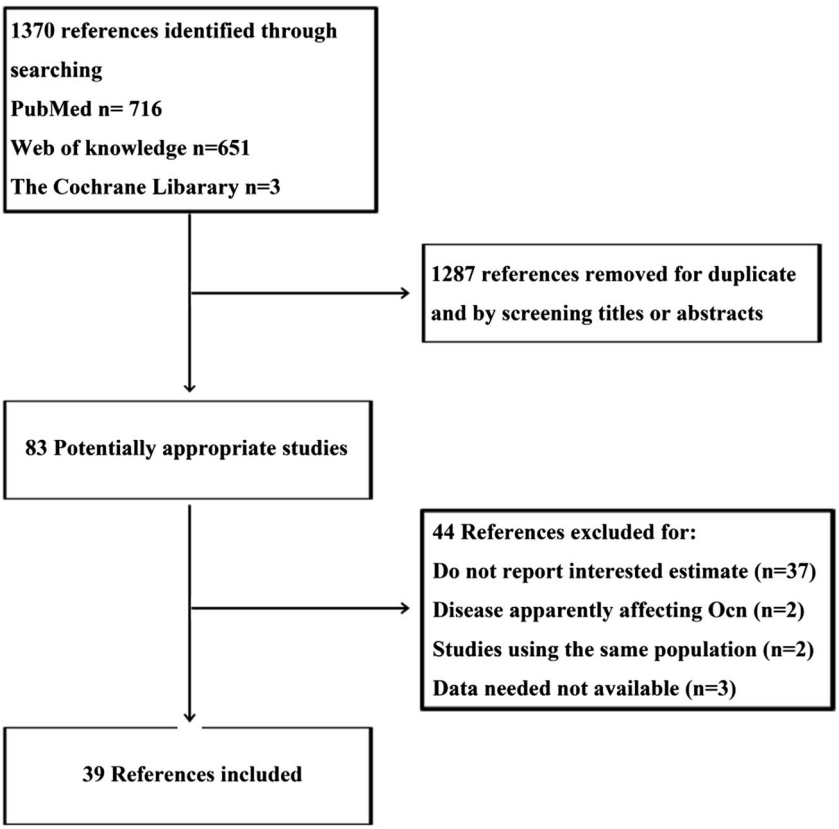

Fig. 1 Flowchart of selected references

Table 1 Characteristics of individual studies included in the meta-analysis

First author, year (reference)	Ethnicity	Gender	Age (year)	Glucose tolerance status[c]	Sample size	*r* value with FPG		*r* value with HbA1c	
						tOcn	unOcn	tOcn	unOcn
Im JA, 2008 [7]	East Asian	Postmenopausal	~57	NGT+IFG+T2DM	339	−0.195		−0.219	
Kindblom JM, 2009 [4]	Caucasian	Men	75.3±3.2	NGT+diabetes	1010	−0.250			
Zhou M, 2009 [5]	East Asian	Men+women	23–76	NGT+T2DM	500	−0.148[a]		−0.175[a]	
Kim SH, 2010 [10]	East Asian	Men	20–76	Nondiabetes	86	−0.056			
Saleem U, 2010 [6]	Black	Men+women	63.5±9.3	Nondiabetes+T2DM	1095	−0.157[a]			
	Caucasian	Men+women	58.7±10.1	Nondiabetes+T2DM	1181	−0.146[a]			
Zhang Y, 2010 [11]	East Asian	Men+women	39–85	Nondiabetes+T2DM	461	−0.062[a]		−0.094[a]	
Aoki A, 2011 [24]	East Asian	Men+women	47.6±10.2	NGT+IGR+T2DM	55	0.250			
Bae SJ, 2011 [8]	East Asian	Men	56.5±7.9	NGT+IFG+T2DM	198	−0.282		−0.277	
	East Asian	Postmenopausal	57.4±6.4	NGT+IFG+T2DM	369	−0.150		−0.239	
Bao YQ, 2011a [9]	East Asian	Men	64.9±10.7	NGT+IGR+T2DM	181	−0.331[a]		−0.220[a]	
Bao YQ, 2011b [25]	East Asian	Men+women	55.0±9.1	T2DM	59	−0.308		−0.317	
Garcia-Martin A, 2011 [26]	Caucasian	Postmenopausal	56.1±3.5	NGT+IFG+T2DM	54	−0.339			
Kanazawa I, 2011[d] [14]	East Asian	Men	59.1±12.8	T2DM	180	−0.220	−0.19	−0.210	−0.270
	East Asian	Postmenopausal	67.2±9.3	T2DM	109	−0.100	−0.18	−0.200	−0.210
Levinger I, 2011[d] [27]	Caucasian	Men	52.4±1.2	NGT+IGR+T2DM	28		−0.548[a]		−0.385[a]
Iki M, 2012[d] [28]	East Asian	Men	73.0±5.2	NGT+T2DM	1597	−0.125	−0.204	−0.142	−0.228
Lee SW, 2012 [15]	East Asian	Postmenopausal	55.7±5.1	Non-T2DM	214	−0.076			
Movahed A, 2012 [29]	Caucasian	Postmenopausal	58.7±7.5	Nondiabetes+T2DM	382	−0.250			
Ngarmukos C, 2012[e] [30]	Thailander	Men	35–55	Nondiabetes	126	−0.270	−0.07		
Wieczorek-Baranowska A, 2012 [31]	Caucasian	Postmenopausal	~65	Nondiabetes	44	−0.395[a]			
Wiklund P, 2012 [32]	Caucasian	Men	20–32	Not defined	50	−0.210			
Alfadda AA, 2013[e] [33]	Caucasian	Men+women	52.5±9.6	T2DM	203			−0.200	−0.090
Bao YQ, 2013 [34]	East Asian	Men	53.8±8.6	NGT+IGR+T2DM	1768	−0.203		−0.168	
Bezerra dos Santos Magalhães K, 2013 [35]	Brazilian	Men+women	41.1±8.4	Not defined	58	−0.348			
Buday, B, 2013[b] [12]	Caucasian	Men	42.0±13.0	NGT+IGR+T2DM	155	−0.067[a]		−0.086[a]	
	Caucasian	Women	49.0±9.0	NGT+IGR+T2DM	135	−0.116[a]		−0.058[a]	
Chen L, 2013 [36]	East Asian	Men	61.5±8.3	NGT+IGR+T2DM	782	−0.087			
	East Asian	Postmenopausal	68.9±7.9	NGT+IGR+T2DM	946	−0.010			
Dou J, 2013 [37]	East Asian	Men	54.0±8.6	NGT+IGR+T2DM	1558	−0.191[a]		−0.122[a]	
Furusyo N, 2013[d] [38]	East Asian	Men	49–62	Not defined	1373		−0.153[a]		−0.148[a]
	East Asian	Women	49–61	Not defined	2285		−0.083[a]		−0.007[a]
Liao M, 2013 [16]	East Asian	Men	20–69	NGT+IGR+T2DM	2400	−0.084			
Liu JM, 2013 [39]	East Asian	Women	20–75	NGT	504	−0.174[a]			
Ogawa-Furuya, N, 2013[d] [40]	East Asian	Men	64.3±8.4	T2DM	118	−0.216	−0.125	−0.173	−0.136
	East Asian	Postmenopausal	64.6±9.7	T2DM	100	−0.089	−0.102	−0.146	−0.131
Schwetz V, 2013[b, e] [41]	Caucasian	Men	31–41	Nondiabetes	152	−0.028[a]	−0.133[a]	−0.137[a]	−0.134[a]
Sheng L, 2013 [42]	East Asian	Men+women	61.5±11.6	T2DM	817	−0.089[a]		−0.024[a]	
Wang QQ, 2013[f] [43]	East Asian	Men+women	51.9±13.3	T2DM	66		−0.278	−0.277	
Weiler HA, 2013 [44]	Mixed	Women	45.3±13.6	Not defined	368	−0.200		−0.230	
Caglar GS, 2014 [13]	Caucasian	Postmenopausal	54.7±5.3	Nondiabetes	87	−0.085[a]			
Chen X, 2014[e] [45]	East Asian	Men	Middle aged	NGT+IGR+T2DM	160	−0.216	−0.137		
Choudhury AB, 2014 [46]	Indian	Premenopausal	44.7±5.9	T2DM	51	−0.486			
	Indian	Postmenopausal	57.8±4.1	T2DM	47	−0.434			

Table 1 (continued)

First author, year (reference)	Ethnicity	Gender	Age (year)	Glucose tolerance status[c]	Sample size	*r* value with FPG		*r* value with HbA1c	
						tOcn	unOcn	tOcn	unOcn
Cui R, 2014 [47]	Asian	Men	60.3±13.6	T2DM	98	−0.171		−0.209	
Maddaloni E, 2014 [48]	Caucasian	Men+women	39.9±12.3	T1DM	93			−0.094[a]	
Rui XF, 2014 [49]	Asian	Men+women	68.0±10.4	T2DM	739	−0.209[a]		−0.232[a]	
		Men	66.8±10.2	T2DM	311	−0.237[a]		−0.322[a]	
		Postmenopausal	68.9±10.5	T2DM	428	−0.169[a]		−0.171[a]	

tOcn total osteocalcin, *unOcn* undercarboxylated osteocalcin, *HbA1c* glycated hemoglobin A1c, *Postmenopausal* postmenopausal women, *Premenopausal* premenopausal women, *NGT* normal glucose tolerance, *IFG* impaired fasting glucose, *IGR* impaired glucose regulation, *T2DM* type 2 diabetes mellitus, *TDM* type 1 diabetes mellitus

[a] *r* values were converted from spearman correlation coefficients

[b] Data were kindly supplied by the corresponding author

[c] Studies performed in subjects with metabolic syndrome were defined as "NGT+IGR+T2DM"

[d] unOcn was quantified by electrochemiluminescence immunoassay from Sanko Junyaku Co., Ltd

[e] unOcn was quantified by enzyme immunoassay from Takara Bio Inc

[f] unOcn was quantified by enzyme-linked immunosorbent assay from R&D system

between tOcn and FPG or HbA1c. The combined association ranged from −0.16 (95 % CI, −0.19 to −0.13) to −0.17 (95 % CI, −0.19 to −0.14) for FPG and varied from −0.16 (95 % CI, −0.19 to −0.13) to −0.17 (95 % CI, −0.19 to −0.15) for HbA1c. However, after excluding the study of Furusyo et al. [38], which was conducted in a Japanese population living in northern Kyushu with low vitamin K intake (vitamin K is essential for the carboxylation of osteocalcin), the heterogeneity in the unOcn group disappeared both for FPG and HbA1c, although the results did not change, with the overall estimates fluctuating from a low of −0.14 (95 % CI, −0.18 to −0.09) to a high of −0.17 (95 % CI, −0.21 to −0.14) between unOcn and FPG, and −0.14 (95 % CI, −0.21 to −0.064) to −0.18 (95 % CI, −0.22 to −0.14) between unOcn and HbA1c.

Subgroup analysis

The populations were stratified according to ethnicity and gender and a subgroup analysis was conducted to explore whether either contributed to the heterogeneity. A fixed-effects model was performed in subgroups with I^2 lower than 50 %, while random-effects model was employed in subgroups with significant heterogeneity ($I^2 \geq 50$ %) (Table 2). Significant negative associations were found in different subgroup populations between tOcn and FPG or HbA1c without significant differences between the groups (Table 2). While, the combined effect size between unOcn and FPG was statistically lower in women than that in men ($r=-0.09$, 95 % CI, −0.13 to −0.05; $r=-0.18$, 95 % CI, −0.21 to −0.14, respectively; P for interaction<0.05) (Table 2). Regarding to the correlation of unOcn and HbA1c, our result showed that there was no statistical difference between men and women (P for interaction>0.05), although a significant association was observed in men ($r=-0.19$, 95 % CI, −0.24 to −0.14) rather than women ($r=-0.09$, 95 % CI, −0.22 to 0.04) (Table 2). The association between unOcn and FPG was significant in East Asians with correlation coefficient −0.15 (95 % CI, −0.20 to −0.10), while in Caucasians, the r value was −0.34 (95 % CI, −0.67 to 0.13) (P for interaction>0.05) (Table 2).

Publication bias

Both Begg's and Egger's test were used to evaluate the potential publication bias. No obvious publication bias was found regarding the included studies evaluating the relationship between total- or unOcn and FPG or HbA1c. For FPG, the Begg's test P values for tOcn and unOcn were 0.257 and 0.837, respectively; For HbA1c, the Begg's test P values for tOcn and unOcn were 0.785 and 0.858, respectively.

Discussion

The main findings of our current meta-analysis are that both circulating tOcn and unOcn are negatively correlated with FPG and HbA1c with similar potency, and the associations between unOcn and glucose metabolism appears to be more prominent in men than in women.

In recent years, genetic and pharmacological studies in mice models suggested that Ocn can promote insulin secretion, improve insulin sensitivity, and improve glucose

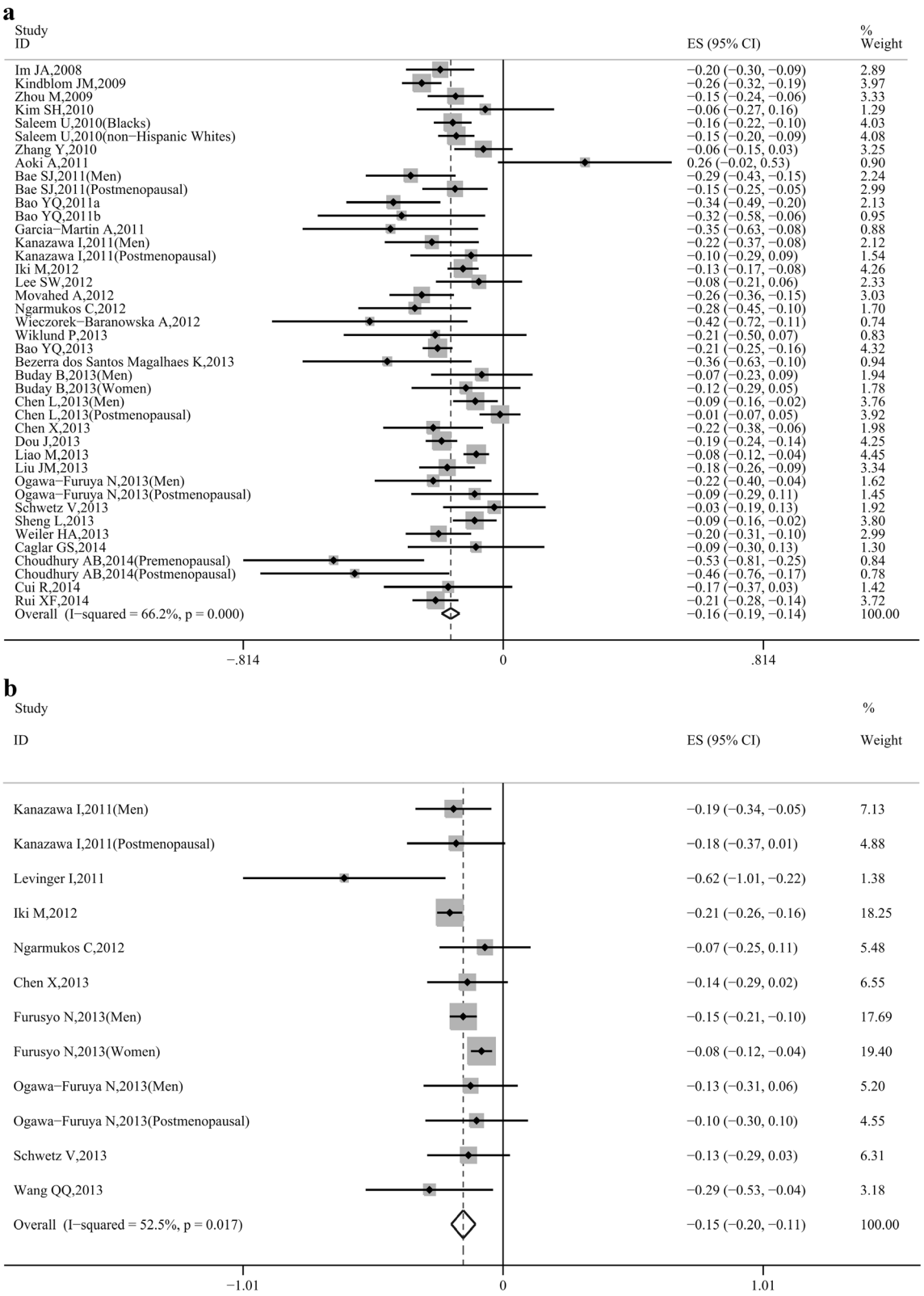

Fig. 2 Correlation (95 % CI) between tOcn (**a**) or unOcn (**b**) and FPG from a random-effects model

tolerance [1]. In addition, mice lacking Ocn receptor Gprc6a specifically in the beta cell lineage displayed glucose intolerance resulting from reduced insulin production [50]. In mice studies, it was also repeatedly demonstrated that the favorable metabolic effects of Ocn on glucose metabolism are mediated through its undercaboxylated form unOcn [2, 3, 51].

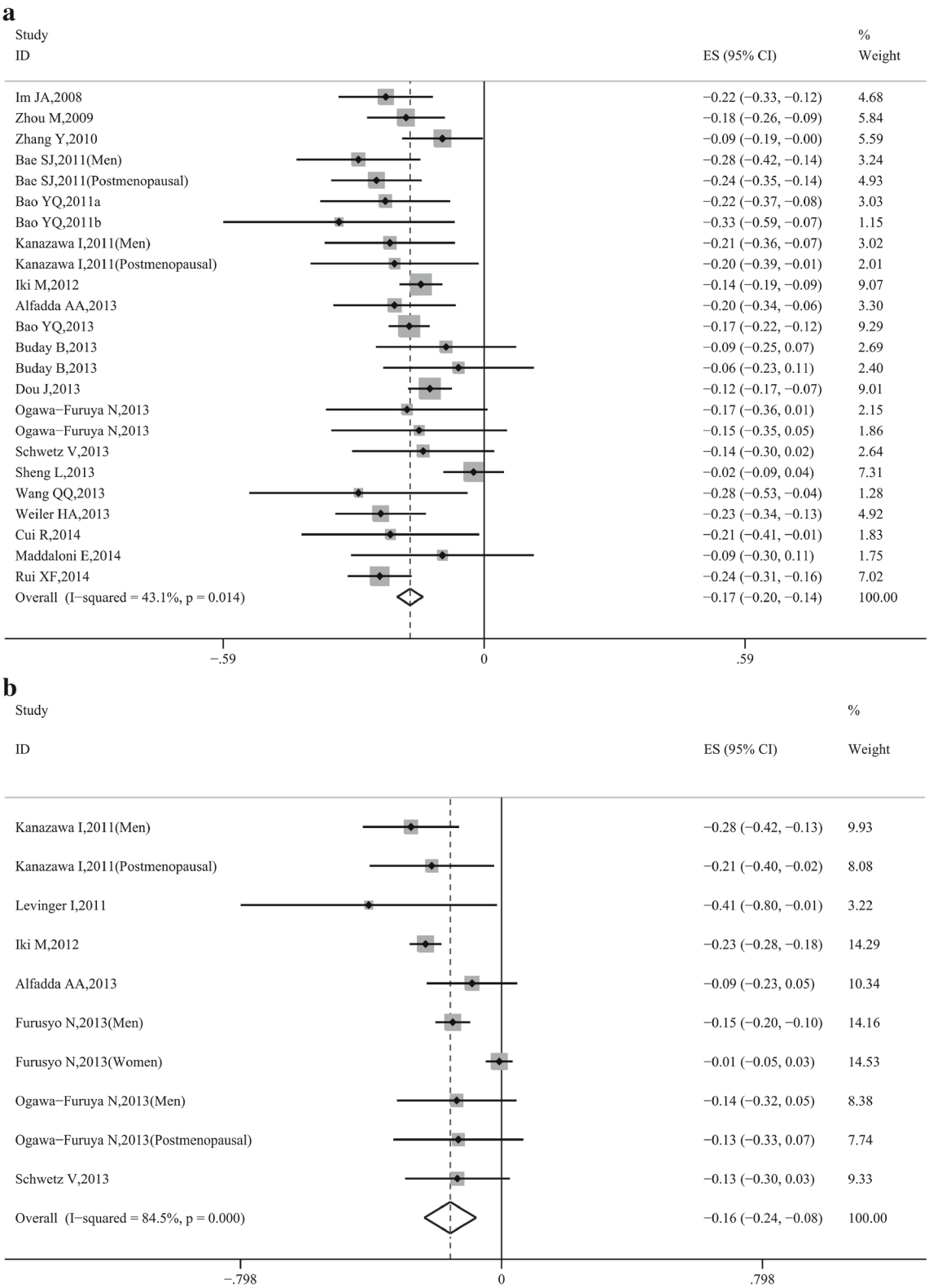

Fig. 3 Correlation (95 % CI) between tOcn (**a**) or unOcn (**b**) and HbA1c from a fix-effects model and random-effects model

Similarly, the majority of human cross-sectional investigations echo the findings in animal studies. In a recent meta-analysis, it also demonstrated that diabetic patients had a significant lower serum tOcn levels as compared with nondiabetes subjects [52], which was consistent with our findings that tOcn was in a negative association with FPG and

Table 2 Correlation between Ocn and glucose metabolism: analysis by gender and ethnicity

Different populations	No. of studies	No. of participants	Estimate size (95 % CI)	*P* value[a]	*P* value[b]	I^2 (%)
tOcn and FPG						
By gender						
Men	18	10,930	−0.18 (−0.22,−0.14)	<0.001	>0.05	69.8
Women	16	4177	−0.18 (−0.23,−0.12)	<0.001		65.5
By ethnicity						
East Asians	25	14,338	−0.14 (−0.18,−0.11)	<0.001	>0.05	68.0
Caucasians	10	3250	−0.18 (−0.24,−0.12)	<0.001		53.7
unOcn and FPG						
By gender						
Men	8	3734	−0.18 (−0.21,−0.14)	<0.001	<0.05	24.0
Women	3	2494	−0.09 (−0.13,−0.05)	<0.001		0.0
By ethnicity						
East Asians	9	5988	−0.15 (−0.20,−0.10)	<0.001	>0.05	52.7
Caucasians	2	180	−0.34 (−0.67, 0.13)	0.154		79.7
tOcn and HbA1c						
By gender						
Men	11	6316	−0.16 (−0. 19,−0.14)	<0.001	>0.05	42.6
Women	7	1848	−0.20 (−0.24,−0.15)	<0.001		0.00
By ethnicity						
East Asians	18	9257	−0.17 (−0.20,−0.14)	<0.001	>0.05	52.0
Caucasians	5	738	−0.12 (−0.20,−0.05)	0.001		0.00
unOcn and HbA1c						
By gender						
Men	6	3448	−0.19 (−0.24,−0.14)	<0.001	>0.05	39.3
Women	3	2494	−0.09 (−0.22, 0.04)	0.190		63.8
By ethnicity						
East Asians	7	5762	−0.16 (−0.25,−0.06)	0.001	>0.05	89.2
Caucasians	3	383	−0.13 (−0.23,−0.03)	0.013		10.0

[a] Intra-group difference

[b] Inter-group difference

HbA1c. As shown in this meta-analysis, both tOcn and unOcn were negatively associated with FPG and HbA1c levels in humans, showing possible involvement of Ocn in glucose homeostasis.

It is noteworthy that there is some controversy regarding the best assay to use for unOcn measurement [53, 54]. Serum unOcn can be measured either by hydroxyapatite (HAP) binding assay, in which the result is reported semi-quantitatively as a fraction of tOcn, or by ECLIA or ELISA methods directly as an absolute value [53, 55]. It was shown that serum unOcn is highly correlated with circulating tOcn concentrations [56, 57], while the serum percentage of unOcn does not correlate with tOcn that much [56]. In this meta-analysis, all the enrolled studies presented the absolute unOcn values. In addition to this technical issue, when analyzing the relations of unOcn with glucose- and obesity-related parameters, the potential confounders, such as age, gender, estrogen levels, food or vitamin K intake, and etc., should all be considered [54, 56, 58, 59].

In the current analysis, the association between tOcn and FPG or HbA1c was similar to unOcn and FPG or HbA1c. Indeed, tOcn and unOcn levels are highly correlated [53, 56, 57]; it is thus expected that at least under normal circumstances (i.e., vitamin K sufficiency), tOcn levels are a good indicator of unOcn concentrations. Therefore, although unOcn was regarded as a metabolically active form of Ocn in mice, in humans, as inferred from our current study, both tOcn and unOcn could be used as biomarkers related with glucose metabolism. The present results were further supported by a recent study that higher tOcn and unOcn were both related with lower diabetes risk [60].

In this meta-analysis, we also found that the magnitude of the correlation between unOcn and glucose metabolism appears to be greater in men than in women, which is consistent

with several studies [8, 14, 38, 40]. The mechanism for such a finding is not clear. Ocn has been demonstrated to induce testosterone production by the testes in male mice [61], while in both rodents and human studies, it was shown that testosterone can protect against streptozotocin- or glucotoxicity-induced β cell apoptosis, especially in male rats [62, 63], and alleviate insulin resistance and improve glycemic control in hypogonadic type 2 diabetic men [64]. However, a most recent systematic review and meta-analysis of randomized controlled clinical trials failed to demonstrate the effects of testosterone treatment on glycemic control in male patients with type 2 diabetes and metabolic syndrome [65]. It is also not clear whether the correlation between unOcn and glucose metabolism observed only in males but not in females is overestimated. It was reported that serum unOcn concentrations were influenced by menopausal status [66], but the majority of studies involved in this meta-analysis did not distinguish the postmenopausal women from the total group. It is thus necessary to further investigate the underlying mechanism or the impacts of the interplay between tOcn, unOcn, and gonadal hormones on glucose metabolism in males and females separately.

In this study, we found that the correlation between unOcn and FPG appears to be significant in East Asians, but not in Caucasians. This result should be interpreted with caution. It should be noted that in the current analysis, only two studies with a very small number of Caucasian participants (n=180) were included. In addition, a significant heterogeneity was observed, which further biased the summary effects. Therefore, confirming the association between unOcn and FPG in Caucasians will require additional studies with a larger sample size.

The current study shows no evidence of publication bias as measured by all of the methods (funnel plot, Begg's and Egger's tests). Whereas, significant heterogeneity was detected among the studies included; a random-effects model was applied to address this problem; subgroup analysis was further performed to deal with it. A possible reason for the heterogeneity among the studies may be due to the discrepancy of ethnicity and gender. In addition, the sample size, duration of diabetes mellitus, drugs taken for glycemic control, age, BMI, and statistic methods may also contribute to the heterogeneity in this meta-analysis.

Some limitations of our current study should be mentioned. First, we did not explore whether the associations between Ocn and FPG or HbA1c are different among nondiabetics, prediabetes, type 2 diabetes mellitus, and type 1 diabetes mellitus. Second, the studies with no significant results tend to be unpublished. This situation, to a certain extent, tends to overestimate the pooled estimate. Moreover, the inadequate inclusion of pertinent references threatens the validity of meta-analysis. Third, the present analysis was conducted entirely with cross-sectional studies reporting the correlation coefficients between Ocn and FPG or HbA1c, where association does not mean causation.

In general, our current meta-analysis agrees with rodent studies which demonstrated a beneficial effect of Ocn on glucose metabolism [1–3], and provided further evidence to demonstrate a negative association between Ocn and FPG and HbA1c in humans. This correlation appears to be more obvious in men than in women for unOcn; however, the causality between Ocn and glucose metabolism calls for prospective studies with larger sample sizes.

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Conflicts of interest Dong-mei Liu, Xing-zhi Guo, Hai-jun Tong, Bei Tao, Li-hao Sun, Hong-Yan Zhao, Guang Ning, and Jian-min Liu declare that they have no conflict of interest.

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