Association of glucose homeostasis and metabolic syndrome with knee cartilage defects and cartilage volume in young adults

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Abstract

Objective To describe the associations of glucose homeostasis and metabolic syndrome (MetS) measures with knee cartilage defects and cartilage volume in young adults.

Methods Fasting blood biochemistry, waist circumference and blood pressure measures were collected 4-5 years prior to knee magnetic resonance imaging (MRI) scans. Blood measures included levels of glucose, insulin, triglyceride and high-density lipoprotein cholesterol (HDL-C). Homeostatic model assessment 2-insulin resistance (HOMA2-IR), HOMA2-beta cell function (HOMA2-β), HOMA2-insulin sensitivity (HOMA-S) and MetS were calculated or defined. Knee cartilage defects and cartilage volume were measured from MRI scans. Data were analysed using log binomial or linear regressions.

Results Among 328 participants (47.3% were females, aged 26-36 years at baseline), 40 (12.7%) had hyperglycaemia and 21 (6.7%) had MetS. Glucose homeostasis measures (except fasting glucose) were associated with tibiofemoral cartilage defects (fasting insulin: relative risk (RR) 1.05, 95% confidence interval (CI) 1.01 to 1.08; HOMA2-IR: 1.44, 1.08 to 1.92; HOMA2-β: 2.59, 1.33 to 5.07; HOMA2-S: 0.36, 0.18 to 0.72), but not patellar cartilage defects. There were no associations between glucose homeostasis measures and knee cartilage volume. High waist circumference (RR 2.32, 95% CI 1.18 to 4.54) and low HDL-C (RR 1.99, 95% CI 1.08 to 3.69) were associated with tibiofemoral cartilage defects, but no other associations were observed between MetS or its components and cartilage defects or volume.

Conclusion Insulin resistance, high waist circumference and low HDL-C were associated with higher risk of tibiofemoral cartilage defects, suggesting glucose homeostasis and some MetS components may affect early cartilage damage in young adults.

Keywords glucose homeostasis; metabolic syndrome; knee cartilage; young adults

Introduction

Knee osteoarthritis (OA) is a common joint disease worldwide, which causes severe knee pain, stiffness and dysfunction [1]. Currently, there are no proven therapies which can arrest or delay disease progression. Thus, identifying the risk factors of knee OA in early life could be important for disease prevention [2].

Magnetic resonance imaging (MRI) is a sensitive technique for examining early structural changes in knee joint [3], including imaging biomarkers of knee OA such as cartilage defects and loss of cartilage volume [4]. Cartilage defects and loss of cartilage volume have been associated with knee pain [5, 6] and subsequent knee replacement surgery [7, 8] in observational studies, and were set as important endpoints in clinical trials [9, 10]. Therefore, preventing knee cartilage defects and loss of cartilage volume may be an effective way to prevent knee OA.

Diabetes mellitus (DM) and OA coexist in the general population [11]. Experimental studies demonstrated that hyperglycaemia can decrease transport of dehydroascorbate into chondrocytes, which then compromises synthesis of type II collagen and leads to cartilage destruction [12]. Additionally, hyperglycaemia is associated with higher inflammatory responses in OA chondrocytes [13], which is detrimental to articular cartilage. A recent systematic review reported that there is limited evidence from epidemiological studies to support an independent association between DM and knee OA. However, the review stressed the requirement for prospective studies, which use objective and appropriate measures for both DM and OA and account for important confounding factors, such as age, sex and body mass index (BMI), to examine the independent associations [14].

Metabolic syndrome (MetS), defined as central obesity, dyslipidaemia, impaired fasting glucose and hypertension, has recently attracted interest in knee OA research as MetS shares many causal pathways with knee OA [15]. Although previous narrative reviews summarised several potential pathophysiologic pathways between MetS and knee OA [16-18], a recent systematic review found insufficient data from epidemiological studies to confirm the links between MetS and knee OA [19]. The systematic review suggested the need for future studies, which account for weight or BMI and examine early stage of disease [19].

Therefore, using data from a cohort of young adults with knee structures measured by MRI, we aimed to describe the associations of glucose homeostasis and MetS measures with knee cartilage defects and cartilage volume.

Methods

Participants

The Childhood Determinants of Adult Health (CDAH) Study was conducted on a nationwide sample of young adults in Australia. During 2004-2006, participants attended clinics which were located at sites in major cities and regional centres around Australia. Measures of anthropometrics, glucose homeostasis, metabolic syndrome (MetS) and physical activity were collected during the clinic visit [20]. The CDAH Knee Cartilage Study was a subsequent sub-study of the CDAH study where participants completed knee MRI scans during 2008-2010.

We used the following strategy to recruit participants from the CDAH study. Participants residing in metropolitan Melbourne and Sydney were contacted by mail and were invited to participate in the CDAH Knee Cartilage Study. Participants who agreed to participate were

assessed for eligibility. Exclusion criteria included being pregnant, having had diseases that might affect knee cartilage (including rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and psoriatic arthritis), or having MRI contraindications. The remaining participants were asked to have an MRI scan at Epworth Hospital in Melbourne or North Shore Private Hospital in Sydney.

This study was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee (HREC), the Monash University HREC and the Northern Sydney and Central Coast Area Health HREC. All participants provided written informed consent.

Anthropometric measurements

Weight was measured to the nearest 0.1 kg (with shoes and bulky clothing removed) using Heine scales (Heine, Dover, NH). Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer (Invicta, Leicester, UK). BMI was calculated as weight in kilograms divided by height in meters squared.

Glucose homeostasis measurements

Fasting glucose and insulin levels were measured using venous blood samples collected from the antecubital vein after a 12-hour fast. An Olympus AU5400 automated analyser (Olympus Optical, Tokyo, Japan) was used to enzymatically measure fasting glucose. A microparticle enzyme immunoassay kit (AxSYM; Abbot Laboratories, Abbot Park, IL) or an electrochemiluminescence immunoassay (Elecsys Modular Analytics E170; Roche Diagnostics, Mannheim, Switzerland) with inter-assay standardisation was used to measure fasting insulin. Glucose homeostasis measures, including homeostatic model assessment 2-insulin resistance (HOMA2-IR), HOMA2-beta cell function (HOMA2-β) and HOMA2-

insulin sensitivity (HOMA-S), were calculated by a homeostasis model assessment (HOMA2) calculator (version 2.2.3 available from http://www.dtu.ox.ac.uk/homacalculator) using fasting glucose and fasting insulin.

MetS measurements

MetS was defined using the harmonized definition [21]. Five components of MetS and their thresholds were proposed in the definition. MetS was diagnosed when at least three of the five components were present. The details of MetS definition and thresholds of MetS components have been published elsewhere [21]. We use the following methods to collect the MetS measures: Waist circumference was measured at the narrowest point between the lower costal border and the iliac crest to the nearest 0.1 cm using a constant tension tape; high waist circumference was defined as waist circumference ≥102 cm in males or ≥88 cm in females. Fasting glucose was measured as described above; hyperglycaemia was defined as fasting glucose of ≥5.6 mmol/L. Triglyceride and high-density lipoprotein cholesterol (HDL-C) were measured enzymatically using an Olympus AU5400 automated analyser (Olympus Optical, Tokyo, Japan). Hypertriglyceridemia was defined as serum triglycerides ≥1.7 mmol/L, and low HDL-C was defined as HDL-C <1.03 mmol/L in males or <1.3 mmol/L in females. Resting systolic and diastolic blood pressure readings were recorded after 5 minutes of quiet sitting using an OMRON HEM907 Digital Automatic Blood Pressure Monitor (Omron Healthcare Co., Ltd., Kyoto, Japan), and the mean of three recordings was used. Hypertension was defined as blood pressure ≥130/85 mmHg.

Physical activity measurements

Physical activity was assessed using the long version of the International Physical Activity Questionnaire. Participants were asked to report the total time (minutes) and frequency

(times/week) of occupational, commuting, domestic and leisure activity during the past week. Physical activities were calculated by multiplying frequency by duration to represent minutes per week of vigorous, moderate and walking activity. Time spent in each domain was summed to provide the estimate of total minutes of physical activity.

MRI measurements

MRI scans were obtained from 2 hospitals, which used the same type of machine (General Electric Medical Systems, Milwaukee, WI, USA). Knees were imaged on a 1.5 T whole-body magnetic resonance unit with use of a commercial transmit-receive extremity coil. The following image sequences were used: (1) a T1-weighted, fat-suppressed 3-dimensional (3D) spoiled gradient-recalled acquisition in the steady state; flip angle 55°; repetition time 58 msec; echo time 12 msec; field of view 16 cm; 60 partitions; 512×512-pixel matrix; acquisition time 11 min, 56 s; 1 acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.31 mm (512×512 pixels). (2) Proton density-weighted fat-suppressed two-dimensional fast spin-echo coronal images at a partition thickness of 3.3 mm and an in-plane resolution of 0.31×0.31 mm (512×512 pixels); repetition time 3800 msec; echo time 45 msec.

Knee cartilage defects were measured as previously reported [22] in an ordinal scale using the T1-weighted spoiled gradient-recalled sagittal MR images and proton density-weighted fast spin-echo coronal MR images together. Grade 0 indicated a normal cartilage. Grade 1 indicated focal blistering and low-signal intensity area in T1-weighted sagittal images or high-signal intensity area in proton density-weighted images with intact surface/bottom. Grade 2 indicated a loss of thickness of <50% on surface/bottom of the cartilage. Grade 3 represented a loss of thickness >50%. Grade 4 indicated a full-thickness chondral wear with

exposure of subchondral bone. A prevalent cartilage defect was defined as a cartilage defect score of $\geqslant$2 at any site within that compartment. Intraobserver reliability expressed as an intraclass correlation coefficient ranged from 0.89 to 0.94.

Cartilage volume was determined by means of 3D image processing on an independent work station using software program OsiriX (Geneva, Switzerland). Individual plates were isolated by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. These data were then re-sampled by means of bilinear and cubic interpolation (area of 312×312 μm^2 and thickness of 1.5 mm, continuous sections) for the final 3D rendering. The coefficients of variation for cartilage volume measures were 2.1-2.6%. Femoral cartilage volume was not measured, as it strongly correlates with tibial cartilage volume [23].

Statistical analyses

Histograms and Q–Q plots were used to assess the normality of continuous variables. Mean (standard deviation), median (interquartile range), and number (percentage) were used to describe normally-distributed variables, skewed variables and categorical variables, respectively. T-tests, Wilcoxon rank-sum test and Chi-square tests were used to assess differences in normally-distributed variables, skewed variables and categorical variables between groups, respectively. Univariable and multivariable log binomial regression models were used to estimate relative risk (RR) for associations of glucose homeostasis and MetS measures with knee cartilage defects before and after adjustment for potential confounders. Univariable and multivariable linear regression models were used to estimate β coefficients for associations of glucose homeostasis and MetS measures with knee cartilage volume before and after adjustment for potential confounders. Age, sex, BMI (except when high

waist circumference was the predictor) and total physical activity were included as potential confounders based on biological plausibility. A p-value less than 0.05 (2-tailed) was considered statistically significant. All statistical analyses were performed in Stata (Texas, USA), version 15.0.

Results

2410 participants completed clinic visit during the CDAH Study and 330 participants completed MRI scans during the CDAH Knee Cartilage Study. The follow-up time was 4-5 years. Nonparticipation in the CDAH Knee Cartilage Study was related to the following: not residing in Melbourne or Sydney (1646), not responding or refusing (235), pregnant (8), rheumatoid arthritis (2), MRI contraindication (13), withdrawal (68), long distance for traveling to the imaging site (103), work/family commitments (3), moving interstate (2). In the current study, 322 participants were included in analyses for cartilage defects and 328 for cartilage volume, as 8 scans were unreadable for cartilage defects and 2 for cartilage volume.

Participants were aged 31-41 (mean 35.4) years when MRI was acquired, 155 (47%) were female. 40 (12.7%) participants had hyperglycaemia and 21 (6.7%) had MetS. Participants included in the current study did less physical activity and had higher fasting glucose and lower HOMA2-β than those in the remainder of the CDAH Study, whereas other characteristics were comparable (Table 1).

Higher fasting insulin, HOMA2-IR and HOMA2-β were significantly associated with higher risk of tibiofemoral cartilage defects and higher HOMA2-S was associated with lower risk of tibiofemoral cartilage defects before and after adjustment for age, sex, BMI and physical activity (Table 2). Fasting glucose was not associated with tibiofemoral cartilage defects.

Glucose homeostasis measures, including fasting glucose, fasting insulin, HOMA2-IR, HOMA2- β and HOMA2-S, were not associated with patellar cartilage defects in either univariable or multivariable analyses (Table 2).

Glucose homeostasis measures were not significantly associated with cartilage volume in univariable analyses, except for the positive associations between fasting glucose and cartilage volume in patella and tibia, and the negative association between HOMA2-β and tibial cartilage volume (Table 3). Associations were no longer significant after adjustment for age, sex, BMI and physical activity (Table 3).

MetS and its components were not associated with patellar cartilage defects in univariable analyses, except hypertriglyceridemia was associated with higher risk of patellar cartilage defects (Table 4); however, this association was no longer statistically significant after adjustment for age, sex, BMI and physical activity (Table 4). MetS and its components were not associated with tibiofemoral cartilage defects in univariable analyses, except for the association between low HDL-C and higher risk of tibiofemoral cartilage defects (Table 4). The significant association persisted and the association between high waist circumference and higher risk of tibiofemoral cartilage defects became significant after adjustment for confounders (Table 4).

MetS and its components were not significantly associated with cartilage volume in univariable analyses, except for the positive associations of hyperglycaemia and hypertension with tibial cartilage volume (Table 5). After adjustment for age, sex, BMI and physical activity, the significant associations disappeared (Table 5).

Discussion

This is the first study describing associations of glucose homeostasis and MetS measures with knee cartilage defects and cartilage volume in young adults. Our major findings were that higher levels of fasting insulin, HOMA2-IR and HOMA2-β were associated with an increased risk of tibiofemoral cartilage defects, and higher level of HOMA2-S was associated with a decreased risk of tibiofemoral cartilage defects. In addition, high waist circumference and low HDL-C were associated with higher risk of tibiofemoral cartilage defects.

Most previous studies describing the association between serum glucose and knee OA have focused on the incidence of radiographic OA (according to Kellgren-Lawrence grade) [14], except for two studies setting T2-relaxation time [24] or cartilage volume [25] as the outcome by using MRI. In one study, self-reported DM was associated with higher baseline T2 (more severe cartilage degradation), but not progression of T2 over 2 years [24]. In the other study, serum glucose (measured 10-14 years prior to baseline MRI) was associated with higher annual loss of tibial cartilage volume over 2 years in females but not in males [25]. Both studies used inaccurate glucose measures (self-reported or measured a long time ago) and did not measure serum insulin. In addition, the populations of interest in these studies were middle-aged or older-aged (40-69 years), whereas no studies were conducted in young adults.

In our study, we used both fasting glucose and fasting insulin, and calculated measures of insulin resistance, beta cell function and insulin sensitivity using the HOMA2 calculator, which is an effective tool to assess glucose homeostasis in clinical and epidemiological studies [26]. We collected MRI-based cartilage measures from young adults, which can predict knee OA and even joint replacement surgery in later life. Our findings that worse glucose homeostasis measures (except for fasting glucose) were associated with higher risk of

tibiofemoral cartilage defects suggested the detrimental effects of insulin resistance on knee cartilage. The lack of association for fasting glucose may be due to the age of our cohort. Young adults may have increased insulin secretion and insulin resistance, whereas their fasting glucose levels could still be in healthy range [27]. Furthermore, we only found significant associations in the tibiofemoral compartment, but not in the patella. The underlying reason was unclear, but may reflect the fact that pathological mechanisms involved in patellofemoral OA and tibiofemoral OA are different [28]. We did not find consistent associations between glucose homeostasis measures and knee cartilage volume; this may be due to knee cartilage defects occurring prior to cartilage volume loss in early knee OA [29].

Previous studies did not find independent associations between MetS and radiographic knee OA cross-sectionally [30] or longitudinally [31]. There is only one study that used a MRI-based outcome (compositional MRI outcome but not structural MRI outcome), which reported participants with $\geqslant$3 metabolic components (versus <3) had higher baseline T2-relaxation time (more severe cartilage degradation) [24]. However, the study used self-reported DM and fat consumption (calculated from food questionnaire) to represent impaired glucose tolerance and dyslipidaemia; in addition, though the study selected the younger half of the source cohort, the participants were middle-aged or older-aged (45-60 years).

Our study addressed the issues in the previous study by using MRI-based structural outcomes in young adults and objective measures of MetS components. We found high waist circumference and low HDL-C were associated with higher risk of tibiofemoral cartilage defects. These results are consistent with previous studies, where central obesity was associated with thinner cartilage thickness in young adults [32] and reduced HDL was

associated with knee OA in mice models [33]. We did not find associations between MetS and cartilage defects or cartilage volume. The reason may be that our participants were young adults (31-41 years) and the prevalence of MetS was low (6.7%). We speculate that MetS will be associated with knee OA when the prevalence of MetS increases with ageing, though this needs to be confirmed by future studies.

Strengths of our study include the selection of a population-based sample of young adults and the use of knee MRI-based structural measures of cartilage. We also used objective measures of glucose homeostasis and MetS. Some limitations of our study should be considered. First, we only had a modest sample size from two urban centres in Australia (as opposed to the coverage of all Australian states/territories in CDAH study), so the generalizability of study results may be limited. We compared characteristics between participants in current study and in the remainder of CDAH Study: the current sample did less physical activity and had higher fasting glucose and lower HOMA2-β. The effects of these differences on our results were unknown though the differences were relatively small. Second, we did not acquire baseline MRI, so we were unable to describe longitudinal changes in knee cartilage defects and cartilage volume. Third, we did not collect knee alignment data, so we were unable to assess its potential effects on our findings.

In conclusion, insulin resistance, high waist circumference and low HDL-C were associated with higher risk of tibiofemoral cartilage defects, suggesting glucose homeostasis and some MetS components may affect early cartilage damage in young adults.

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Author contributions Study conception and design: TM, BA, AV, FC, LM, TD, GJ and CD; acquisition of data: TM, BA, AV, FB, FC, LM, MC, TD, GJ and CD; analysis and interpretation of data: TM, BA, AV, FB, FC, LM, MC, TD, GJ, LL and CD. All authors participated in the preparation of manuscript, approved the manuscript for submission and publication, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declarations of interest: none

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Table 1. Characteristics of the participants in current study and the remainder of original study

	MRI measures		P value
	Yes (n=328)	No (n=2002)	
Age [a] (years)	30.8 (2.7)	31.1 (2.6)	0.138
Female, n (%)	155 (47.3)	1037 (51.5)	0.150
BMI (kg/m^2)	25.3 (4.1)	25.8 (4.9)	0.090
Total physical activity (hour/week), median (IQR)	9.6 (5.6, 15.7)	11.1 (6.3, 17.9)	**0.017**
Glucose homeostasis measures, median (IQR)			
Fasting glucose (mmol/L)	5.1 (4.8, 5.3)	5.0 (4.7, 5.3)	**0.017**
Fasting insulin (mU/L)	5.8 (4.2, 7.9)	6.0 (4.3, 8.7)	0.207
HOMA2-IR (unit)	0.80 (0.60, 1.10)	0.80 (0.60, 1.20)	0.146
HOMA2-β (unit)	0.79 (0.66, 1.00)	0.85 (0.68, 1.06)	**0.005**
HOMA2-S (unit)	1.27 (0.95, 1.69)	1.23 (0.86, 1.67)	0.168
MetS measures, n (%)			
MetS	21 (6.7)	136 (7.2)	0.744
High waist circumference [b]	36 (11.3)	293 (14.6)	0.121
Hyperglycaemia [c]	40 (12.7)	195 (10.3)	0.192
Hypertriglyceridemia [d]	49 (15.6)	280 (14.8)	0.716
Low HDL-C [e]	52 (16.5)	371 (19.6)	0.201
Hypertension [f]	60 (18.4)	436 (21.7)	0.169
Cartilage defects, n (%)			
Patellar	78 (24.2)		
Tibiofemoral	47 (14.6)		
Cartilage volume (mm^3)			
Patellar	2939 (752)		
Tibial	3896 (1005)		

Values are mean (SD) unless otherwise stated.
Bold denotes statistical significance, $p<0.05$.
MRI, magnetic resonance imaging; BMI, body mass index; HOMA2-IR, homeostatic model assessment 2-insulin resistance; HOMA2-β, homeostatic model assessment 2-beta cell function; HOMA2-S, homeostatic model assessment 2-insulin sensitivity; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; MetS, metabolic syndrome.
[a]Age in Childhood Determinants of Adult Health Study.
[b]Defined as waist circumference ≥102 cm in males or ≥88 cm in females.
[c]Defined as fasting glucose ≥5.6 mmol/L.
[d]Defined as serum triglycerides ≥1.7 mmol/L.
[e]Defined as HDL-C <1.03 mmol/L in males or <1.3 mmol/L in females.
[f]Defined as blood pressure ≥130/85 mm Hg.

Table 2. Associations between glucose homeostasis measures and knee cartilage defects

	Univariable RR (95% CI)	Multivariable[a] RR (95% CI)
Patellar		
Fasting glucose, mmol/L	0.62 (0.37 to 1.03)	0.55 (0.29 to 1.04)
Fasting insulin, mU/L	0.99 (0.94 to 1.04)	0.95 (0.88 to 1.02)
HOMA2-IR, per unit	0.90 (0.61 to 1.33)	0.60 (0.32 to 1.14)
HOMA2-β, per unit	1.10 (0.61 to 1.96)	0.87 (0.38 to 1.99)
HOMA2-S, per unit	1.01 (0.70 to 1.45)	1.15 (0.76 to 1.75)
Tibiofemoral		
Fasting glucose, mmol/L	1.31 (0.72 to 2.40)	0.89 (0.41 to 1.93)
Fasting insulin, mU/L	**1.05 (1.02 to 1.07)**	**1.05 (1.01 to 1.08)**
HOMA2-IR, per unit	**1.42 (1.15 to 1.76)**	**1.44 (1.08 to 1.92)**
HOMA2-β, per unit	**2.13 (1.24 to 3.65)**	**2.59 (1.33 to 5.07)**
HOMA2-S, per unit	**0.46 (0.27 to 0.78)**	**0.36 (0.18 to 0.72)**

Bold denotes statistical significance, $p<0.05$.
[a]Adjusted for age, sex, body mass index and physical activity.
CI, confidence interval; HOMA2-IR, homeostatic model assessment 2-insulin resistance; HOMA2-β, homeostatic model assessment 2-beta cell function; HOMA2-S, homeostatic model assessment 2-insulin sensitivity; RR, relative risk.

Table 3. Associations between glucose homeostasis measures and knee cartilage volume (mm^3)

	Univariable β (95% CI)	Multivariable[a] β (95% CI)
Patellar		
Fasting glucose, mmol/L	**255.2 (60.6 to 449.7)**	-92.9 (-293.3 to 107.4)
Fasting insulin, mU/L	-2.6 (-21.3 to 16.1)	-6.3 (-25.1 to 12.4)
HOMA2-IR, per unit	1.1 (-154.6 to 156.9)	-40.6 (-195.9 to 114.7)
HOMA2-β, per unit	-228.8 (-513.6 to 56.0)	-48.0 (-330.5 to 234.5)
HOMA2-S, per unit	9.5 (-151.9 to 171.0)	32.4 (-125.6 to 190.4)
Tibial		
Fasting glucose, mmol/L	**561.2 (307.6 to 814.8)**	-22.0 (-280.0 to 236.1)
Fasting insulin, mU/L	-4.9 (-29.7 to 19.9)	-17.5 (-41.5 to 6.6)
HOMA2-IR, per unit	-15.3 (-221.5 to 190.8)	-127.8 (-323.1 to 67.6)
HOMA2-β, per unit	**-463.2 (-838.1 to -88.4)**	-236.8 (-592.0 to 118.4)
HOMA2-S, per unit	19.8 (-193.9 to 233.6)	64.9 (-134.3 to 264.1)

Bold denotes statistical significance, $p<0.05$.
[a]Adjusted for age, sex, body mass index and physical activity.
CI, confidence interval; HOMA2-IR, homeostatic model assessment 2-insulin resistance; HOMA2-β, homeostatic model assessment 2-beta cell function; HOMA2-S, homeostatic model assessment 2-insulin sensitivity.

Table 4. Associations between metabolic syndrome measures and knee cartilage defects

	Univariable RR (95% CI)	Multivariable[a] RR (95% CI)
Patellar		
MetS	1.37 (0.72 to 2.60)	1.38 (0.60 to 3.21)
High waist circumference [b]	1.44 (0.86 to 2.39)	1.13 (0.59 to 2.15)
Hyperglycaemia [c]	0.91 (0.50 to 1.68)	0.76 (0.32 to 1.78)
Hypertriglyceridemia [d]	**1.66 (1.08 to 2.55)**	1.66 (0.97 to 2.84)
Low HDL-C [e]	0.93 (0.55 to 1.60)	0.88 (0.48 to 1.61)
Hypertension [f]	1.15 (0.72 to 1.84)	1.23 (0.70 to 2.17)
Tibiofemoral		
MetS	2.06 (0.99 to 4.29)	1.39 (0.58 to 3.32)
High waist circumference [b]	1.86 (0.98 to 3.54)	**2.32 (1.18 to 4.54)**
Hyperglycaemia [c]	1.24 (0.60 to 2.57)	0.90 (0.37 to 2.14)
Hypertriglyceridemia [d]	1.32 (0.68 to 2.56)	0.89 (0.40 to 1.96)
Low HDL-C [e]	**2.45 (1.43 to 4.19)**	**1.99 (1.08 to 3.69)**
Hypertension [f]	1.57 (0.86 to 2.84)	1.50 (0.77 to 2.95)

Bold denotes statistical significance, $p<0.05$.
[a]Adjusted for age, sex, body mass index (except when high waist circumference was the predictor) and physical activity.
[b]Defined as waist circumference ≥102 cm in males or ≥88 cm in females.
[c]Defined as fasting glucose ≥5.6 mmol/L.
[d]Defined as serum triglycerides ≥1.7 mmol/L.
[e]Defined as HDL-C <1.03 mmol/L in males or <1.3 mmol/L in females.
[f]Defined as blood pressure ≥130/85 mmHg.
CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; RR, relative risk.

Table 5. Associations between metabolic syndrome and knee cartilage volume (mm^3)

	Univariable β (95% CI)	Multivariable[a] β (95% CI)
Patellar		
MetS	131.1 (-205.0 to 467.3)	-116.2 (-432.4 to 199.9)
High waist circumference [b]	-82.7 (-345.9 to 180.4)	20.1 (-213.0 to 253.2)
Hyperglycaemia [c]	212.8 (-37.3 to 462.9)	-64.1 (-306.5 to 178.2)
Hypertriglyceridemia [d]	119.7 (-111.5 to 350.9)	-52.0 (-170.9 to 275.0)
Low HDL-C [e]	-33.1 (-259.2 to 192.9)	-20.5 (-221.7 to 180.8)
Hypertension [f]	90.2 (-121.1 to 301.5)	-188.7 (-380.4 to 3.1)
Tibial		
MetS	210.1 (-234.8 to 655.1)	-255.7 (-660.2 to 148.8)
High waist circumference [b]	-218.2 (-566.4 to 130.0)	-120.7 (-418.9 to 177.4)
Hyperglycaemia [c]	**438.5 (108.4 to 768.6)**	-55.8 (-367.5 to 255.9)
Hypertriglyceridemia [d]	165.9 (-140.2 to 472.0)	-154.0 (-439.3 to 131.4)
Low HDL-C [e]	2.4 (-297.0 to 301.8)	-109.2 (-366.9 to 148.6)
Hypertension [f]	**333.7 (53.6 to 613.7)**	-38.4 (-285.4 to 208.6)

Bold denotes statistical significance, $p<0.05$.
[a]Adjusted for age, sex, body mass index (except when high waist circumference was the predictor) and physical activity.
[b]Defined as waist circumference ≥102 cm in males or ≥88 cm in females.
[c]Defined as fasting glucose ≥5.6 mmol/L.
[d]Defined as serum triglycerides ≥1.7 mmol/L.
[e]Defined as HDL-C <1.03 mmol/L in males or <1.3 mmol/L in females.
[f]Defined as blood pressure ≥130/85 mmHg.
CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; RR, relative risk.