META-ANALYSIS

Gamma glutamyltransferase and metabolic syndrome risk: a systematic review and dose–response meta-analysis

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SUMMARY

Aims: We aimed to quantify and characterise in detail the nature of the dose–response relationship between baseline gamma glutamyltransferase (GGT) level and risk of incident metabolic syndrome (MetS) in the general population and determine the precise estimate of the magnitude of the association. Methods: We performed a systematic review and dose–response meta-analysis of published prospective cohort studies. Relevant studies were identified in a literature search of MEDLINE, EMBASE and Web of Science up to May 2014. A potential nonlinear relationship between GGT levels and MetS was examined using restricted cubic splines. Study-specific estimates were combined using random-effects models. Results: Of the 323 studies reviewed, we included 10 prospective cohort studies with data on 67,905 participants comprising of 6595 incident MetS cases. In pooled analysis of seven studies with relevant data, baseline GGT level was statistically significantly positively associated with risk of MetS in a nonlinear fashion (p for nonlinearity = 0.003). Comparing individuals in the top vs. bottom thirds of baseline GGT levels, relative risk for MetS in pooled analysis of all 10 eligible studies was 1.88 (95% confidence interval: 1.49–2.38). Evidence was lacking of publication bias among the contributing studies. Conclusion: Baseline GGT level is positively and strongly associated with risk of the MetS in a nonlinear dose–response manner.

Introduction

The Third Report of the National Cholesterol Education Program – Adult Treatment Panel (NCEP-ATP) III has stressed the importance of targeted preventive approaches for individuals with the metabolic syndrome (MetS) (1), given that these patients are at increased risk of type 2 diabetes (2,3) and cardiovascular disease (CVD) (2,4). Gamma glutamyltransferase (GGT) and alanine aminotransferase (ALT), common markers of liver dysfunction, have been linked to the development of the MetS. There has been considerable uncertainty regarding the nature and magnitude of their prospective associations until recently. Liu et al. (5) synthesised available prospective epidemiological data on the association between ALT and incident MetS and reported a strong association. We have also recently demonstrated a linear dose–response relationship between ALT and risk of MetS (6). In a recent review (7) published in an issue of The International Journal of Clinical Practice, the authors reported a multivariate adjusted relative risk (RR) (95% confidence interval) of 1.63 (1.43–1.82) for MetS in a comparison of the highest vs. lowest category of baseline GGT levels. They reported a 9% increase in the risk of the MetS per 5 U/l increment in GGT level in dose–response analysis, therefore assuming a linear relationship. Detailed characterisation of the nature of any dose–response relationship is however lacking, as this was not addressed by this review and previous studies. It is not clear if there is a clear linear relationship with the association across the whole range of GGT levels or there is a threshold effect. It is important to establish this, especially if there exists a threshold which would potentially optimise the detection of individuals at increased risk of the MetS. In addition, the previous review did not standardise the reported risk estimates (they reported comparisons comparing the highest vs. lowest category of GGT levels irrespective of the risk estimates the eligible studies reported) to a consistent comparison, thereby limiting the validity
of the results. Finally, since the publication of this review, a number of studies have been published on the topic. Against this background, we report an updated analysis which aims to quantify and characterise in detail the nature of the dose–response relationship between GGT level and risk of MetS. We also conducted subsidiary analyses to obtain a precise estimate of the magnitude of the association, by standardising reported risk estimates from eligible studies to a consistent comparison (top vs. bottom thirds of baseline levels of GGT).

Methods

Data sources and searches
This review was conducted using a predefined protocol and reported in accordance with PRISMA and MOOSE guidelines (Appendices S1–2) (8). We searched MEDLINE, EMBASE and Web of Science electronic databases up to May 2014, for prospective (cohort, case-cohort or ‘nested case control’) population-based studies reporting on the associations between baseline circulating GGT level and MetS risk. The computer-based searches combined free and MeSH search terms and combination of key words related to GGT (e.g. ‘gamma glutamyltransferase’) and MetS (e.g. ‘metabolic syndrome’). There were no restrictions on language or the publication date. Reference lists of retrieved articles were manually scanned for all relevant additional studies and review articles. We restricted the search to studies of humans. Further details on the search strategy are presented in Appendix S3.

Study selection
Observational cohort studies were included if they had at least 1 year of follow-up, assessed associations of GGT with incident MetS in adults, with samples measured at baseline, and recruited participants from approximately general populations (i.e. they did not select participants on the basis of confirmed preexisting medical conditions such as MetS, diabetes mellitus, or known liver diseases at baseline). For the assessment of dose–response analysis, studies that reported RRs with 95% confidence intervals (CIs) for at least three quantitative GGT categories were eligible.

Data extraction and quality assessment
Data were abstracted, where available, on study, publication date, geographical location, population source, time of baseline survey, sample population, study design, sample source (plasma/serum), nature of sample (fresh or frozen and storage temperature), assay type and source, sample size, numbers of MetS outcomes, MetS case definition, mean age at start of study, duration of follow-up and degree of adjustment for potential confounders (defined as ‘+’ when RRs were adjusted for age and/or sex; ‘++’ further adjustment for potential risk factors such as blood pressure, body mass index, smoking status, or family history of diabetes; and ‘++++’ additional adjustment for alcohol consumption, other liver enzymes or inflammatory markers). We extracted RRs reported for the greatest degree of adjustment. Two authors (T.A.A. and D.S.) independently abstracted data and performed quality assessments using a standardised predesigned data collection form. Any disagreement regarding eligibility of an article was agreed by consensus with a third reviewer (S.K.K.).

Study quality was assessed based on the nine-star Newcastle–Ottawa Scale (NOS) (9) using predefined criteria namely: selection (population representativeness), comparability (adjustment for confounders) and ascertainment of outcome. The NOS assigns a maximum of four points for selection, two points for comparability and three points for outcome. Nine points on the NOS reflects the highest study quality. A score of ≥ 5 indicated adequate quality for inclusion in the review.

Data synthesis and analysis
The RR with 95% CIs was used as the common measure of association across studies. We used generalised least-squares trend estimation analysis as described by Greenland and Orsini (10,11) to compute the trend from the correlated natural logs of the RRs across categories of GGT. For studies that presented results separately according to subgroups (e.g. by sex), separate dose–response trends were derived and a within-study summary estimate was obtained using a fixed effect analysis. The dose–response trends are presented for a 5 U/l increment in GGT level. We examined a potential nonlinear dose–response relationship between GGT levels and MetS by modelling GGT levels using restricted cubic spline functions with three knots at percentiles 25%, 50% and 75% of the distribution (12). A p-value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero. Study-specific results were combined using random-effects models.

In subsidiary analyses, we pooled the RRs for all identified eligible studies to obtain a precise estimate of the magnitude of the association. To enable a consistent approach to the meta-analysis and enhance interpretation of the findings, reported study-specific risk estimates (per standard deviation change, quintiles and quartiles) were transformed to involve comparisons between the top third and bottom third
of each study population’s baseline distribution of GGT levels, using standard statistical methods (10,13). Briefly, log risk estimates were transformed assuming a normal distribution (or that a transformation of the explanatory variable for which the risk ratio is based was normally distributed), with the comparison between top and bottom thirds being equivalent to 2.18 times the log risk ratio for a one standard deviation increase (or equivalently, as 2.18/2.54 times the log risk ratio for a comparison of extreme quarters and as 2.18/2.80 times the log risk ratio for a comparison of extreme quintiles). Standard errors of the log risk estimates were calculated using published confidence limits and were standardized in the same way. When studies published more than one estimate of the association according to subgroups (e.g. by sex), we obtained a within-study summary estimate using a fixed effect analysis. Summary RRs were pooled using a random effects model to minimise the effect of between-study heterogeneity (14). Statistical heterogeneity was assessed by standard $\chi^2$ and $I^2$ statistics, with $I^2 > 50\%$ considered to be important (15,16). Study-level characteristics including geographical location, sex, average duration of follow-up, number of cases, MetS case definition and degree of adjustment were prespecified as characteristics for assessment of heterogeneity, which was conducted using stratified analysis and random effects meta-regression (17). Evidence of publication bias was assessed using Begg’s funnel plots and Egger’s asymmetry test (18,19). All analyses were performed using Stata release 12 (StataCorp, College Station, TX).

**Results**

**Study identification and selection**

Our initial search identified 323 potentially relevant citations (Figure 1). After screening the titles and abstracts, 30 articles remained for further evaluation. We reviewed and assessed these 30 articles, and excluded 20 articles because they (i) were cross-sectional studies ($n = 6$) (ii) had no relevant exposure or outcome ($n = 13$) (iii) or duplicated a previous publication from the same study ($n = 1$). In sum, this meta-analysis included 10 articles (Appendix S4) based on 10 cohorts, comprising 67,905 participants and 6595 MetS cases.

**Study characteristics and quality**

Table 1 provides details of eligible studies. Mean ages of participants ranged from 37 to 52 years. Majority of studies (seven) were conducted within the Asia region (China, Japan and Korea), two studies from Europe (France and Turkey) and one from North America (USA). Duration of follow-up for the development of MetS ranged from 2.5 to 19 years. Eight studies ascertained the diagnosis of MetS according to NCEP-ATP III criteria (1) (defined previously (6)). Of these eight studies, four studies used body mass index (BMI) instead of waist circumference in their definition of abdominal obesity. Two studies used the International Diabetes Federation criteria (IDF) (20) (also defined previously (6)). The degree of covariate adjustment varied, but all studies adjusted for most of the established risk factors. Overall, we judged all of the included studies to be of high quality (quality score: 7–9). Table S1 provides assay characteristics of measured levels of GGT from studies contributing to the analysis.

**GGT and risk of MetS**

In pooled results of seven studies (nine data points) providing relevant data, there was evidence of a non-linear significant positive association ($p$ for non-linearity = 0.003) between GGT level and risk of MetS (Figure 2). The pooled RR (95% CI) of MetS in a comparison of individuals in the top thirds with those in the bottom thirds of baseline GGT level for all 10 eligible studies was 1.88 (1.49–2.38), with substantial heterogeneity between studies ($I^2 > 70\%$) (Figure 3). The inconsistency among the contributing studies was not explained by any study-level characteristic (Figure 4). Egger’s test was not significant ($p = 0.62$), consistent with observed funnel plot symmetry.

**Discussion**

We have extended the findings of the previous review which assumed a linear dose–response relationship between circulating GGT level and risk of MetS and we have also provided a more precise estimate of the magnitude of the association. Our findings demonstrate that baseline GGT level is associated with MetS in a nonlinear fashion with a steeper increase in MetS risk at GGT levels below approximately 14 U/l. Comparing individuals in the top vs. bottom thirds of circulating GGT levels, there was an approximately 90% increased risk of the MetS.

Though GGT and ALT are biomarkers of liver fat, with ALT being more specific for liver fat content, GGT has been demonstrated to be a better predictor of diabetes than ALT; and this stronger association has been postulated to reflect the association of GGT with several processes related to the pathogenesis of diabetes (21). There are also indications that GGT may be more strongly related to the MetS compared with ALT (22). Plausible mechanisms by which elevated GGT level has been linked to the development
of the MetS involve the same pathways related to the development of diabetes, which include oxidative stress, increased inflammation and excessive deposition of fat in the liver, which are implicated in impaired insulin signalling and insulin resistance (23,24). Similar pathways have been postulated for the positive association between GGT and CVD risk, which has also been demonstrated to exist at normal reference levels of GGT (25). Given that the MetS is a significant risk factor for CVD and a linear association has been demonstrated for GGT and CVD (25); our findings of a nonlinear association between GGT and the MetS appear at first to be at odds with what is expected. The results are however not quite at odds with what is expected. Close inspection of the dose-response shape shows two linear features to it – a steep increase in MetS risk at GGT levels below 14 U/l and a less steep increase in risk at GGT levels above 14 U/l. The limited data points (albeit using published data) precluded us from summarising the dominant linear features using two linear splines, reinforcing the need for further data to characterise the nonlinear relationship of GGT with MetS.

Our findings may have implications for the prevention of the MetS in the general population. The evidence suggests that the risk of the MetS is increased within the so-called normal reference range of GGT levels. The cut-off for the upper normal limit and reference range for GGT has not been clearly defined, and is essentially arbitrary, being determined ideally by enzyme measuring activity in a healthy population and using the central 95% of values obtained from the population (26). A number of physiological or demographical factors (e.g. age,
| Lead author, publication year | Name of study or source of participants | Location of study | Year(s) of baseline survey | Baseline age range (years) | % male | Duration of follow-up | Total no. of participants | No. of cases | MetS case definition | Covariates adjusted for | Study quality |
|-------------------------------|----------------------------------------|------------------|----------------------------|---------------------------|--------|-----------------------|--------------------------|--------------|----------------------|------------------------|-------------|
| Nakanishi, 2004               | Office Workers Japan                   | 1994             | 35–59                      | 100.0                     | 7.0    | 2957                  | 608                      | NCEP-ATP III* | Age, family history of diabetes, BMI, alcohol intake, cigarette smoking, regular physical activity, WBC count, other liver markers |
| Andre, 2007                   | DESIR France                           | 1994–1996        | 30–65                      | 46.7                      | 3.0    | 3545                  | 309                      | IDF         | Age, alcohol intake, PA, smoking, ALT, fasting insulin, HOMA-IR |
| Lee, 2007                     | FHS Offspring HPC United States Korea | 1978–1982        | 44†                        | 48.0                      | 19.0   | 3451                  | 968                      | NCEP-ATP III* | Age, sex, alcohol consumption, CRP |
| Jo, 2009                      | HPC Korea                              | 2002             | 19–86                      | 70.8                      | 4.0    | 21,535                | 802                      | IDF         | Age, alcohol intake, PA, smoking, ALT, HOMA-IR |
| Ryu, 2010                     | Korean Male Workers Korea              | 2002             | ≥ 40                       | 100.0                     | 5.0    | 9148                  | 1056                     | NCEP-ATP III* | Age, BMI, blood pressure, fasting blood glucose, TG, HDL-C, uric acid, regular exercise, alcohol consumption |
| Xu, 2011                      | City of Shanghai China                | 2004–2008        | ≥ 40                       | 60.2                      | 3.5    | 681                   | 180                      | NCEP-ATP III | Age, sex, occupation, educational level, family history of diabetes, smoking, drinking status, leisure-time activity, BMI, HOMA-IR, ALT |
| Oh, 2011                      | Centre for Health Promotion Korea     | 2002/2005        | 48†                        | 56.2                      | 3.0    | 429                   | 46                       | NCEP-ATP III | Age, sex, alcohol drinking status |
| Onat, 2011                    | TARFS Turkey                           | 2003–2004        | 33–84                      | 49.1                      | 4.0    | 975                   | 332                      | NCEP-ATP III | Age, sex, menopause, BMI, alcohol use |
| Suh, 2012                     | Korean Male Office Workers Korea       | 2005/2009        | 41†                        | 100.0                     | 4.0    | 15,109                | 1113                     | NCEP-ATP III* | Age, alcohol drinking status, smoking |
| Tao, 2013                     | MJ HMC China                           | 2003/2010        | 41†                        | 51.0                      | 2.5    | 10,076                | 1181                     | NCEP-ATP III | Age, sex, current smoking, drinking, PA, BMI, family history of CVD, SBP, WBC, HDL-C, fasting glucose, TG, CRP |
| **Total**                     |                                        |                  |                            |                           |        | 67,905                | 6595                     |             |                      |                        |             |

DESIR, Data from Epidemiological Study on the Insulin Resistance Syndrome; FHS, Framingham Heart Study; HPC, Health Promotion Centre; MJ HMC, MJ Health Management Centers; TARFS, Turkish Adult Risk Factor Study; ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; IDF, International Diabetes Federation; MetS, metabolic syndrome; NCEP-ATP III, National Cholesterol Education Program-Adult Treatment Panel III; TG, triglycerides; WBC, white blood cell. *Used BMI instead of waist circumference in their definition of abdominal obesity. †Mean age at baseline.
Figure 2 Dose–response relationship between gamma glutamyltransferase level and relative risk of the metabolic syndrome. Adjusted relative risks and 95% confidence intervals (CIs; dashed lines) are reported. Gamma glutamyltransferase levels were modelled with restricted cubic splines with three knots in a random-effects dose–response model. The median value (4.5 U/l) of the lowest reference range was used to estimate all relative risks. The vertical axis is on a log scale.

| Author, year of publication | No. of cases | Degree of adjustment† | RR (95% CI)          |
|-----------------------------|--------------|-----------------------|----------------------|
| Oh, 2011                    | 46           | ++                    | 3.68 (1.07, 12.67)   |
| Xu, 2011                    | 180          | +++                   | 2.04 (1.17, 3.54)    |
| Andre, 2007                 | 309          | +++                   | 1.80 (1.23, 2.63)    |
| Onat, 2011                  | 332          | +++                   | 1.41 (1.10, 1.80)    |
| Nakanishi, 2004             | 608          | +++                   | 1.87 (1.38, 2.53)    |
| Jo, 2009                    | 802          | +++                   | 3.07 (2.20, 4.29)    |
| Lee, 2007                   | 968          | +++                   | 1.62 (1.38, 1.92)    |
| Ryu, 2010                   | 1056         | +++                   | 1.27 (1.03, 1.56)    |
| Suh, 2012                   | 1113         | +++                   | 3.13 (2.58, 3.80)    |
| Tao, 2013                   | 1181         | +++                   | 1.41 (1.10, 1.80)    |
| Overall                     |              |                       | 1.88 (1.49, 2.38)    |

Figure 3 Prospective studies of gamma glutamyltransferase levels and the metabolic syndrome. The summary estimate presented was calculated using a random effects model; †, Degree of adjustment; +, adjusted for age and/ or sex; ++, further adjustment for potential risk factors; +++ additional adjustment for alcohol consumption, other liver markers or inflammatory markers; Size of data markers are proportional to the inverse of the variance of the relative ratio; CI, confidence interval (bars); GGT, gamma-glutamyltransferase; RR, relative risk
body mass index, race, physical activity etc.) affect GGT levels (27), making the definition of a reference range very complicated. There are significant gender differences, with males having higher levels than females; and the reference ranges set by laboratories also vary as these depend on the assays used and several studies have reported different cut-offs for the upper limit of normal (25,28,29). However, over several decades ago, the recommended cut-off for the upper normal limit of GGT was set at an average of 51 U/l for men and 33 U/l for women (30). Though GGT is not very specific for the liver, mild and subtle elevations in GGT levels below these upper limits of normal are very common in the general population and may indicate the presence of subclinical liver disease – most commonly nonalcoholic fatty liver disease (also known as the hepatic manifestation of the MetS (31)). Assays for GGT are less specific for the liver compared with ALT, but they are also sensitive, well standardised, simple, inexpensive and commonly measured as part of routine liver function panels. Based on the current data, it is likely that assays for GGT have the potential to improve the identification of individuals at high risk of developing the MetS, a strong risk factor for CVD (2,4). Further study is however required to establish these potential roles. In the absence of such data, persistent elevations of GGT levels below the recommended upper limits of normal in individuals should be a cue for further clinical evaluation.

Figure 4   Associations of gamma glutamyltransferase with risk of the metabolic syndrome, grouped according to several study characteristics. The summary estimates presented were calculated using random effects models; Size of data markers is proportional to the inverse of the variance of the relative ratio; CI, confidence interval (bars); GGT, gamma glutamyltransferase; IDF, International Diabetes Federation; NCEP-ATP III, National Cholesterol Education Program-Adult Treatment Panel III; RR, relative risk; *p-value for meta-regression

| Subgroup                           | No. of participants | No. of cases | RR (95% CI) | P-value* |
|------------------------------------|--------------------|--------------|-------------|----------|
| **Location**                       |                    |              |             |          |
| Europe                             | 4,520              | 641          | 1.52 (1.22, 1.90) | .68      |
| North America                      | 3,451              | 968          | 1.62 (1.37, 1.91) |          |
| Asia                               | 59,934             | 4,986        | 2.07 (1.46, 2.94) |          |
| **Sex**                            |                    |              |             |          |
| Males                              | 49,336             | 2,978        | 2.49 (1.41, 4.41) | .31      |
| Females                            | 25,079             | 302          | 1.68 (0.91, 3.12) |          |
| Both                               | 18,569             | 3,315        | 1.59 (1.41, 1.79) |          |
| **MetS case definition**           |                    |              |             |          |
| NCEP-ATP III                       | 42,826             | 5,484        | 1.78 (1.37, 2.31) | .33      |
| IDF                                | 25,079             | 1,111        | 2.37 (1.41, 4.00) |          |
| **Average follow up, years**       |                    |              |             |          |
| >/= 5                              | 15,556             | 2,632        | 1.54 (1.26, 1.89) | .23      |
| < 5                                | 52,349             | 3,963        | 2.10 (1.50, 2.92) |          |
| **No. of cases,**                  |                    |              |             |          |
| >/= 500                            | 62,275             | 5,728        | 1.92 (1.40, 2.63) | .84      |
| < 500                              | 5,630              | 867          | 1.67 (1.31, 2.13) |          |
| **Study quality**                  |                    |              |             |          |
| 9                                  | 4,226              | 489          | 1.87 (1.37, 2.56) | .97      |
| < 9                                | 63,679             | 6,106        | 1.88 (1.44, 2.47) |          |

RR (95% CI) top versus bottom third of baseline GGT levels

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confounder adjustment across individual studies. Majority of studies, however, adjusted for potential confounders. It was not possible to achieve a comparable outcome definition of MetS across all studies, as different case definitions for MetS (NCEP-ATP III or IDF) were used; however, majority of studies used NCEP-ATP III criteria, with only two studies using IDF criteria. The NCEP-ATP III and IDF definitions have also been found to show good agreement in the diagnosis of MetS (32,33). In addition, subgroup analysis by MetS case definition showed consistent associations. There was substantial heterogeneity among the contributing prospective studies, which we systematically explored using stratified analyses, meta-regression and sensitivity analyses. We presented pooled RRs for prespecified subgroups and the results showed that the strong positive association demonstrated for GGT and MetS risk was generally consistent across all subgroups.

In conclusion, available evidence suggests a positive nonlinear dose–response association of baseline GGT level with risk of the MetS.

Author contributions

S.K.K. researched data, analysed data and wrote the manuscript. T.A.A. and D.S. contributed to data collection, reviewed and edited the manuscript. S.K.K. is the guarantor and had full access to all the data in the study and takes responsibility for the integrity of the data and the decision to submit and publish the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

- **Appendix S1.** PRISMA 2009 check list.
- **Appendix S2.** MOOSE check list.
- **Appendix S3.** Literature search strategy.
- **Appendix S4.** Reference list of included studies.

Table S1. Study and assay characteristics of studies contributing data to current analysis.

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