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Review

Fasting insulin, insulin resistance and risk of hypertension in the general population: A meta-analysis

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ABSTRACT

Background: Studies on the association of fasting insulin concentrations or insulin resistance with subsequent risk of hypertension have yielded conflicting results.
Objective: To quantitatively assess the association of fasting insulin concentrations or homeostasis model assessment insulin resistance (HOMA-IR) with incident hypertension in a general population by performing a meta-analysis.
Methods: We searched the PubMed and Embase databases until August 31, 2016 for prospective observational studies investigating the elevated fasting insulin concentrations or HOMA-IR with subsequent risk of hypertension in the general population. Pooled risk ratio (RR) and 95% confidence interval (CI) of hypertension was calculated for the highest versus the lowest category of fasting insulin or HOMA-IR.
Results: Eleven studies involving 10,230 hypertension cases were identified from 55,059 participants. Meta-analysis showed that the pooled adjusted RR of hypertension was 1.54 (95% CI 1.34–1.76) for fasting insulin concentrations and 1.43 (95% CI 1.27–1.62) for HOMA-IR comparing the highest to the lowest category. Subgroup analysis results showed that the association of fasting insulin concentrations with subsequent risk of hypertension seemed more pronounced in women (RR 2.07; 95% CI 1.19–3.60) than in men (RR 1.48; 95% CI 1.17–1.88).
Conclusions: This meta-analysis suggests that elevated fasting insulin concentrations or insulin resistance as estimated by homeostasis model assessment is independently associated with an exacerbated risk of hypertension in the general population. Early intervention of hyperinsulinemia or insulin resistance may help clinicians to identify the high risk of hypertensive population.

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1. Introduction

Hypertension is one of the most common public health concern worldwide. The total number of adults with hypertension is expected to rise to 1.56 billion by 2025 [1]. The burden of hypertension in China is high and increasing [2] and approximately 33.6% of adults suffer from hypertension [3]. Hypertension risk prediction based on conventional risk factors such as age, sex, body weight, dietary sodium intake, alcohol consumption, and cigarette smoking remains inadequate. Therefore, identification of new predictors of hypertension is necessary for the clinical practice.

Fasting insulin concentrations reflect the state of glucose metabolism. Hyperinsulinemia is considered a marker of insulin resistance [4]. Insulin resistance is defined as the inability of insulin to increase cellular glucose uptake and utilization, leading to compensatory hyperinsulinemia [5]. Several epidemiological studies [6–13] but not in all study [14] showed that increased fasting insulin level or insulin resistance was associated with subsequent risk of hypertension. A well-designed meta-analysis [15] has confirmed the association of higher fasting insulin concentrations and greater risk of hypertension. However, this meta-analysis did not assess the effects of insulin resistance on hypertension risk and perform gender-specific analysis of fasting insulin concentrations. Ever since then, some new publications [16–18] instigated our efforts to conduct an updated meta-analysis using the available clinical evidence.

To the best of our knowledge, no previous meta-analysis has been performed to assess the association of homeostasis model assessment insulin resistance (HOMA-IR) with subsequent hypertension risk. This meta-analysis aimed to assess the association of elevated fasting insulin concentrations or HOMA-IR with subsequent hypertension risk in a general population.

2. Materials and methods

2.1. Search strategy

This meta-analysis was conducted based on the Meta-analysis of Observational Studies in Epidemiology reporting guidelines [19]. A comprehensive literature search of the PubMed and Embase was conducted until August 31, 2016 without language restriction. We used the following search terms in various combinations: “insulin” OR “hyperinsulinemia” OR “insulin resistance” OR “HOMA-IR” AND “hypertension” OR “blood pressure” AND “prospective” OR “follow-up” OR “longitudinal”. Additionally, the references cited in the relevant studies were manually searched to identify any potentially eligible articles.

2.2. Study selection

Eligible studies had to satisfy the following inclusion criteria :1) prospective observational studies that enrolled general population; 2) baseline fasting insulin concentrations or insulin resistance as exposure; and 3) reporting at least age-adjusted risk estimate of hypertension associated with the highest versus the lowest category of fasting insulin concentrations or insulin resistance. Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 and/or diastolic blood pressure (DBP) ≥90 mm Hg (or SBP/DBP ≥ 160/95 mm Hg), use of any antihypertensive medications in combination with a self-report of hypertension. Insulin resistance was estimated using HOMA-IR and calculated by fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5. Data from retrospective studies, cross-sectional designs, conference abstract, or reviews were excluded. When multiple articles were conducted in the same population, we only selected the article with the most complete data.

2.3. Data extraction and quality assessment

Two investigators (F Wang and LL Han) independently extracted the following data from the original articles: surname of the first author, publication year, geographic regions, study design, sample size, gender distribution, mean age or age range, exposure category, most fully adjusted risk ratio (RR) or odds ratio (OR) and their 95% confidence interval (CI), definition of hypertension, number of incident hypertension cases, follow-up duration, adjusted confounding variables. Study quality was evaluated using a nine-star Newcastle–Ottawa Scale (NOS) for cohort studies [20], including three domains of participant selection, comparability of groups, and assessment of outcomes. Studies achieving 6 or more stars were considered high-quality. Any discrepancies in data extraction and quality assessment were resolved by consensus or in consultation with a third investigator.

2.4. Statistical analyses

Risk estimates of individual studies were reported as a HR, OR, or RR. The OR and HR were assumed to approximate the same measure of RR. We pooled the multivariable-adjusted RR and 95% CI of hypertension was calculated for the highest versus the lowest category of fasting insulin or HOMA-IR. Heterogeneity across studies was assessed using the Cochran Q statistic at <0.10 and quantified by the I^2 tests, where $I^2 \geq 50\%$ reflected significant heterogeneity. We used a random effects model if the heterogeneity was observed; otherwise, a fixed-effect model was adopted [21]. We explored the potential publication bias using the Begg's test [24] and Egger's test ($P < 0.10$ was considered statistically significant) [25]. In subgroup analyses, we stratified by the number of participants, ethnicity, gender, fasting insulin value, period of follow-up, definition of hypertension, and adjustment for body weight or family history of hypertension. Sensitivity analysis was carried out to test the stability of the pooling results by removing a single study from the analysis at each time. All analyses were performed by using STATA statistical software 12.0 (Stata, College Station, TX, USA).

3. Results

3.1. Search results and study characteristics

Fig. 1 summarizes the flow diagram of the study selection process. Briefly, a total of 579 articles were identified from the initial literature search. After screening of title and abstract, 511 articles were excluded. Sixty-eight full-text articles were obtained for more detailed evaluation. On the basis of our predefined inclusion criteria, 57 articles were further removed mainly due to not report outcome interesting, irrelevant exposure, or not prospective design. Finally, 11 prospective studies [6–8,10–14,16–18] were eligible for this meta-analysis.

The baseline characteristics of the 11 included studies are shown in Table 1. The total number of participants was 55,059, with study populations ranging from 135 to 25,062 in the individual studies. The follow-up length ranged from 3.16 to 20 years. Ten studies [6–8,10–14,17,18] reported fasting insulin concentrations and five studies [11–13,16,18] reported HOMA-IR. Hypertension was defined as SBP/DBP ≥ 140/90-mm Hg or current use of antihypertensive medications in 7 studies [7, 11–13,16–18]. Four studies [6,8,10,14] defined hypertension by SBP/DBP ≥ 160/95 mm Hg or current use of antihypertensive medications. Four studies [7,8,14,17] consisted of men only, one study [6] only consisted of women, and one study [18] provided outcomes by gender. The overall NOS ranged from 6 to 8 stars, and all studies were grouped as high-quality (Supplemental Table S1).

3.2. Fasting insulin concentrations and risk of hypertension

Ten studies [6–8,10–14,17,18] reported the association of fasting insulin concentrations with subsequent risk of hypertension. As shown in