Hyperglycemia Effects on Blood Pressure in Adults: A Systematic Review and Meta-Analysis

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Abstract

A higher-than-normal blood glucose level characterizes hyperglycemia, the primary metabolic feature of type 2 diabetes mellitus (T2DM) caused by insulin resistance and β-cell dysfunction. As a consequence of tissue or organ damage, hyperglycemia can cause an increase in blood pressure, according to previous research. The paucity of data makes comprehending the relationship between hyperglycemia and elevated blood pressure challenging. A detailed evaluation and meta-analysis were performed to investigate how hyperglycemia influences blood pressure. In addition, this study provides information on hyperglycemia biomarkers associated with the progression of high blood pressure. This investigation utilized a systematic review and a meta-analysis following the PRISMA recommendations. A comprehensive literature search was conducted on relevant literature published between 2012 and 2022, utilizing electronic database systems such as PubMed, ScienceDirect, and Google Scholar. The random effects model was employed to combine odds ratios (OR). The meta-analysis included eleven out of the 23 studies by employing the Review Manager software. This analysis revealed the effects of hyperglycemia and normal blood glucose on blood pressure in adults (OR=2.18; 95% CI, 1.14 to 4.18). The microvascular complication (OR=1.27; 95% CI, 1.20 to 1.35) and arterial stiffness (MD=-5.93; 95% CI, -11.23 to -0.65) are factors that may contribute to the progression of hyperglycemia to high blood pressure. HbA1c was possibly the most effective biomarker for hyperglycemia (MD=1.81; 95% CI, 0.44 to 3.02). In conclusion, hyperglycemia significantly affects BP in adults, and both mechanisms identified, including microvascular complication and arterial rigidity, are associated with elevated BP in a hyperglycemic state.

Keywords
Hyperglycemia, Type 2 Diabetes Mellitus, Blood Pressure, Hypertension, HbA1c, Vascular Stiffness

Introduction

Hyperglycemia is when the glucose concentration in the bloodstream exceeds the normal threshold, specifically surpassing 149 mg/dl (7.8 mmol/L)[1]. Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and dysfunction of β-cells, key metabolic factors[2]. Furthermore, a study revealed a notable coexistence of elevated blood glucose levels and hypertension in the young adult population[3].
Observational and clinical trial data indicate that inpatient hyperglycemia is associated with an increased risk of complications and mortality, a more extended hospital stay, and a higher admission rate to the intensive care unit in patients with or without a prior diagnosis of diabetes. In 2004, approximately 3.4 million people perished due to hyperglycemia\textsuperscript{[4]}.

Hypertension is associated with hyperglycemia over time\textsuperscript{[5]}. It has been observed that youthful adults frequently exhibit high blood glucose and hypertension\textsuperscript{[3]}. Blood pressure is the force exerted by the arteries, the body's primary blood vessels, as blood circulates against the artery walls. Hypertension accounts for approximately 7.5 million fatalities or 12.8% of global mortality\textsuperscript{[4]}.

The hemoglobin A1c (HbA1c) biomarker is commonly used to identify the presence and severity of hyperglycemia. A biomarker is a biological molecule found in blood\textsuperscript{[6,7]}, other body fluids\textsuperscript{[8,9]}, or tissues\textsuperscript{[8]} that indicates whether a condition is normal or abnormal. Glycemic control monitoring requires serum HbA1c measurement, observing the patient's genuine current glycated HbA1c\textsuperscript{[10]}. In addition, other biomarkers include fructosamine\textsuperscript{[11]}, glycated albumin\textsuperscript{[12]}, triglycerides\textsuperscript{[13]}, CRP, IL6, IL18\textsuperscript{[14]}, and others with limitations such as moderate sensitivity and specificity and inaccuracy in certain clinical conditions.

Hyperglycemia is a metabolic disorder caused by defects in the metabolism of carbohydrates, fats, and proteins owing to impaired insulin secretion or action. According to a previous study, hyperglycemia increased in adults due to obesity and declining activity\textsuperscript{[15]}. However, a paucity of available data impedes a complex relationship between hyperglycemia and high blood pressure and the underlying mechanism by which prolonged hyperglycemia affects blood pressure. Subsequently, data regarding the precise factors that affected blood pressure in long-term hyperglycemia are insufficient to determine the factor responsible for the blood pressure increases\textsuperscript{[3,4]}.

**Literature Review**

**Hyperglycemia Affects Blood Pressure**

Hyperglycemia occurs when glucose levels exceed 7.0 mmol/L (126 mg/dl) when fasting and 11.0 mmol/L (200 mg/dl) 2 hours after meals. When the fasting plasma glucose level decreases between 100 and 125 mg/dL, a patient has prediabetes or impaired glucose tolerance\textsuperscript{[16]}. The loss of pancreatic β-cells or the development of insulin resistance causes an increase in blood glucose levels. Many people may not recognize hyperglycemia symptoms until their blood sugar levels significantly increase.

Hyperglycemia typically occurs in individuals with diabetes or prediabetes due to overeating and insufficient physical activity\textsuperscript{[17]}. In addition, hyperglycemia occurs in critically ailing or injured individuals, indicating non-diabetic hyperglycemia. Pancreatic disorders and hormonal imbalances also cause hyperglycemia in individuals with certain health conditions\textsuperscript{[18]}.

By interacting with glucoregulatory hormones, insulin, and counterregulatory hormones such as glucagon, cortisol, catecholamines, and growth hormone, glucose metabolism is maintained. Insulin controls glucose synthesis in the liver by inhibiting gluconeogenesis and glycogenolysis\textsuperscript{[19]}. Insulin promotes protein synthesis\textsuperscript{[20]}, glucose uptake, and glycogen synthesis in insulin-sensitive tissues such as muscle\textsuperscript{[21]} while inhibiting glycogenolysis and protein degradation, depending on blood levels. Insulin inhibits lipolysis, oxidation of free fatty acids, and ketogenesis\textsuperscript{[22]}.

Abnormally elevated hepatic glucose production is the primary pathophysiological issue. Rapid proteolysis and decreased protein synthesis increase the availability of gluconeogenic precursors such as alanine and glutamine, increasing hepatic glucose production. Increasing muscle glycogenolysis is necessary for lactate production, and glycerol production precedes lipolysis\textsuperscript{[22]}.
Hyperglycemia and high blood pressure share common causes and risk factors, and a person with either condition is more likely to develop the other. Hyperglycemia and hypertension are closely associated due to shared risk factors, such as endothelial dysfunction, vascular inflammation, arterial remodeling, atherosclerosis, dyslipidemia, and obesity[23]. Then, elevated blood pressure is associated with an increase in the volume of circulatory fluid and peripheral vascular resistance[24].

Patients with hyperglycemia exhibit increased peripheral arterial resistance due to vascular remodeling and elevated body fluid content due to insulin resistance-induced hyperinsulinemia and hyperglycemia[25]. According to these findings, hypertension is caused by increased fluid content within the body[26]. Similarly, vascular remodeling has progressed in diabetic patients with T2DM after the mid-stage. Peripheral vascular resistance also contributed to hypertension and demonstrated that the risk of hypertension was 1.5 to 2.0 times higher in diabetic patients than non-diabetic patients, whereas approximately one-third of hypertensives develop T2DM[24].

**Microvascular Complication of Hyperglycemia Affects Blood Pressure**

Untreated hyperglycemia has the potential to give rise to a range of life-threatening consequences, one of which is damage to the peripheral vascular system. Hyperglycemia necessitates prompt medical intervention and should be efficiently managed to enhance the prognosis[16].

Stimulating the sympathetic nervous system can influence the regulation of arteriolar constriction and dilatation. The autonomic nervous system[27] regulates blood pressure, a critical factor in modulating short-term fluctuations during stress and physical exertion[27,28].

In addition, the etiology of hypertension is predominantly ascribed to the interaction between the autonomic nervous system and the renin-angiotensin system, in conjunction with other factors such as circulating volume and recently identified hormonal influences[29]. The involvement of epinephrine and norepinephrine can be observed in the pathophysiology of hypertension. Both chemicals are crucial in the body’s physiological response, known as the fight-or-flight response. Upon entering the bloodstream, they elicit increased blood pressure and blood sugar levels[1].

**Potential Biomarker of Hyperglycemia Associated with Blood Pressure**

HbA1c is a blood biomarker to indicate the presence and extent of hyperglycemia[30]. HbA1c is generated by binding glucose to the amino-terminal group of a hemoglobin subunit. A diagnosis of diabetes is determined by an HbA1c level equal to or greater than 6.5% (48 mmol/mol), while prediabetes is indicated by HbA1c levels ranging from 5.7% to 6.4% (39-46 mmol/mol)[31].

Experts have found a correlation between HbA1c levels and mortality and mortality[7]. The HbA1c marker is a more accurate way to identify microvascular complications[32] as they are more effective in assessing chronic glycemic control. Additionally, HbA1c levels offer advantages such as increased convenience, improved stability during pre-analytic processes[23], and reduced fluctuations during periods of stress[34].

**Materials and Methods**

**Study design**

This study is a meta-analysis to evaluate hyperglycemia’s impact on blood pressure levels in adult individuals. Systematic literature reviews adhere to the guidelines set forth by the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) to ensure methodological rigor and comprehensive reporting. The acquisition of research is accomplished through a systematic exploration of electronic databases such as PubMed, ScienceDirect, and Google Scholar. Pertinent and interconnected research is employed to mitigate the potential for an elevated bias percentage within this study. The research was conducted between October 2022 until June 2023.
Research Question Using the PICO Model

The research question for this systematic review and meta-analysis was formulated according to the PICO framework. The PICO framework highlights four elements, i.e., population (P), intervention (I), control (C), and outcome (O), to be included while formulating the research question in a systematic review:

1. What is the mechanism of the hyperglycemia state (intervention) that can progress to blood pressure (outcomes) in adults (population)?
2. What are the potential hyperglycemia biomarkers (intervention) that affect blood pressure (outcome) in adults (population)?

Systematic Literature Review Investigation

A comprehensive literature search was conducted by searching the relevant and related literature from 2012 until 2022 in electronic database platforms such as PubMed, ScienceDirect, and Google Scholar to identify and determine hyperglycemia’s effect on blood pressure in adults. Besides that, the published article was selected only in the English language, full-text and abstract articles were used and analyzed for the next step. The keyword used in this study includes 'effects of hyperglycemia on blood pressure in adults', 'hyperglycemia effects on hypertension', 'mechanism of blood pressure in hyperglycemic state', 'hyperglycemia linked to increasing blood pressure', 'pathophysiology of blood pressure in high blood glucose in adults', and 'hyperglycemia biomarker associated with blood pressure', were used to aid in the finding of outcome in this study.

Study selection

The selection of the study started with a comprehensive search in a systematic review including many studies that fulfill the inclusion and exclusion criteria by using various electronic data platforms such as ScienceDirect, Google Scholar and PubMed. The duplicate studies were eliminated from the literature search to ensure no duplication or overlap of information in this study. However, from the duplicate study, only one was selected for analysis. Next, the title and abstracts were screened manually, whether they were related and relevant to this study before assessing the studies.

Inclusion criteria

The team of investigators employed specific criteria to choose patients with T2DM and hypertension, along with relevant scientific material. Furthermore, the above-mentioned publication was disseminated between 2012 and 2022 to utilise the extracted data that has been verified and authenticated. The inquiry used full-text and abstract sources to obtain the most recent and comprehensive information.

Exclusion criteria

The investigation deliberately excluded another organism, demanding the involvement of a human participant. In addition, this study excluded individuals diagnosed with hyperglycemia who also had cystic fibrosis and pancreatic cancer.

Data Extraction

All the relevant data were extracted, such as year of publication, first author name, study design, primary or secondary causes of hyperglycemia, the hyperglycemia biomarker used associated with high blood pressure, the effect on blood pressure in adults with hyperglycemia and its mechanism, and level of blood pressure either high or normal blood pressure.

Literature Quality Evaluation

Cochrane’s Q and I² statistics were used to measure the heterogeneity. Cochrane's Q statistic is based on a chi-square test, while I² statistics focus on score heterogeneity between 0% and 100%. Then, the forest plot
was applied for bias assessment using funnel plot analysis followed by measuring forest plot asymmetry. The forest plot provides a quick summary of the finding.

**Statistical Analysis**

Meta-analysis was carried out using Review Manager Software, capable of performing a meta-analysis on the data entered and displaying the graft result. The 95% confidence interval (CI) was applied to determine the effect estimates. Therefore, a confidence interval merely assesses how well the sample represents the population under consideration. The confidence level of the CI is the probability that the confidence interval includes the true mean value within a population.

The model employed in this study is the random effect model. Utilizing the random effects model in meta-analysis enables the accommodation of heterogeneity by positing that the effects follow a distribution. Heterogeneity pertains to the variability observed in the outcomes of different studies. The forest was used due to effective graphical displays for summarizing meta-analysis results. The studies included were represented by a box and a horizontal line through the box. Each forest plot has a vertical line, the ‘no effect’ line, corresponding to the value one (1%) for binary outcomes such as OR and 0 for continuous outcomes.

**Results**

**Article Screening**

Before applying any exclusion criteria, 44 articles were identified through online databases such as PubMed, Google Scholar, and Science Direct. After eliminating duplicate articles, 44 unique articles remained in the dataset. Subsequently, 21 articles were excluded based on examining their titles and abstracts, as they were found to have been published outside the designated timeframe of 2012 to 2022. The reviewed article focuses on the secondary complications associated with hyperglycemia. The exclusion of the remaining 12 articles was primarily attributed to their focus on animal subjects and other factors, including incomplete data and irrelevant information concerning the present study. The present meta-analysis comprised a total of 11 articles. The articles selection process is summarized in the PRISMA flow chart (Figure 1).

**Study Characteristic**

Five studies included such as Edeoga et al. (2017), Midha et al. (2015), Sasaki et al. (2020), Wheeler et al. (2020) and Kotruchin et al. (2018) were used to explore the effect of hyperglycemia state that can progress to blood pressure, four articles selected which were from Hurst et al. (2015), Ma et al. (2022), Kobayashi et al. (2021), and Wakasugi et al. (2021) for the mechanism of hyperglycemia effects on blood pressure. Articles from Ma et al. (2022) and Zhao et al. (2021) were used in potential biomarkers that affect the level of blood pressure.

**Risk of Bias within the Study**

An assessment of bias within the included studies was conducted using RevMan Software. Then, the Funnel plot was tested for asymmetry and found to have a minimal risk of publication bias.
Blood Glucose Levels Affect Blood Pressure

The current study seeks to identify four scholarly articles that examine the correlation between blood glucose levels and blood pressure. Among a sample of 6,808 adults, it was observed that 5,240 individuals diagnosed with hyperglycemia experienced an elevation in their blood pressure levels. Among a sample size of 8954 individuals, it was observed that 3988 adults with normoglycemia exhibited normal blood pressure, as depicted in Figure 2. The effects of increased blood pressure in hyperglycemia were statistically significant (OR=2.18; 95% CI, 1.14 to 4.15; p=0.02), with high heterogeneity $I^2=95\%$. 

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Figure 1: PRISMA flow chart
Figure 2: Blood glucose levels affect blood pressure

Based on the forest plot above, the Edeoga et al. 2017 and Midha et al. (2015) are not significant due to the value of 95% CI includes the one at the horizontal axis, and the articles passed through the vertical line marked at one, with OR values of 1.31 (95% CI, 0.96 to 1.78) and 0.5 (95% CI, 0.17 to 1.45), respectively. While the study by Sasaki et al. (2020) and Wheeler et al. (2020) are significant due to the value of 95% CI does not include one, the p-value < 0.05, and does not pass through the vertical line in the forest plot with the OR values of 3.09 (95% CI, 2.84 to 3.37) and 6.01 (95% CI, 4.31 to 8.27), respectively.

Microvascular Complication in Hyperglycemia State Affects Blood Pressure

Two articles demonstrate that the microvascular complication of hyperglycemia leads to an increase in blood pressure (Figure 3). Among 38707 adults, 4748 adults with microvascular complications lead to increases in blood pressure, compared to 2239 adults with non-microvascular complications in hyperglycemia.

Figure 3: Microvascular complication in hyperglycemia state progress to increase blood pressure.

The position of the diamond from the forest plot shows its favor on the microvascular complication contributing to high blood pressure in adults in a hyperglycemia state. The results obtained are shown in Figure 3. The mechanism of microvascular complication in hyperglycemia state progress to increase blood pressure was statistically significant (OR=1.27; 95% CI, 1.20 to 1.35; p<0.00001), with considerably low heterogeneity I²=0%.

Arterial stiffness causes Blood Pressure

Two studies in Figure 4, which were from Kobayashi et al. (2021) and Wakasugi et al. (2021), provide data on the association of arterial stiffness in changing the blood pressure level in adults. There was a statistically significant mean difference (MD) of -5.93 (95% CI, -11.23 to -0.63; p=0.03), with considerably low heterogeneity (I²=45%) found in this analysis.

Figure 4: Arterial stiffness affects blood pressure.
Potential HbA1c Biomarker in High Blood Pressure Prediction

Two studies in Figure 5 provide data on measuring HbA1c biomarkers on different blood pressure levels. The results show the forest plot of the mean difference of HbA1c biomarker measurement on high and normal blood pressure. This analysis is statistically significant with an MD of 1.81 (95% CI, 0.44 to 3.18; p=0.01). However, it has high heterogeneity (I²=97%).

<table>
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<th>Normal Blood Pressure</th>
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Figure 5: Association of HbA1c biomarker and High Blood Pressure

Discussion

Based on the present study's findings, it is evident that Wheeler et al. (2020) have demonstrated a significant association between T2DM and hypertension. Specifically, their analysis reveals that a substantial majority of participants diagnosed with T2DM (98.3%) exhibit a higher likelihood of also having hypertension than participants without T2DM (90.5%). According to the study conducted by Sasaki et al. (2020), a majority of diabetic patients (63.8%) were found to have coexisting hypertension, while a smaller proportion (36.3%) of participants exhibited normal fasting glucose levels. The results presented in this study are substantiated by a meta-analysis of randomized controlled trials, which demonstrated a significant correlation between elevated sugar consumption and increased systolic and diastolic blood pressures[35].

Moreover, this study analyzed a notable disparity in the occurrence of diabetes among participants who developed hypertension (92%) compared to those who did not (38%), and this impact is statistically significant. Hyperglycemia exhibits a 2.18-fold increased likelihood of impacting blood pressure levels in adult individuals. Furthermore, this study demonstrated a potentially significant correlation between hyperglycemia and blood pressure levels. However, due to the presence of high heterogeneity, the meta-analysis conducted was deemed inappropriate.

However, the analysis presented in this study has been verified by a separate study that involved the inclusion of Japanese patients diagnosed with T2DM and no prior record of clinically evident cardiovascular disease. These individuals were selected as participants to examine the relationship between metrics derived from continuous glucose monitoring and arterial stiffness. The data revealed a notable disparity in the prevalence of hypertension among patients with T2DM when comparing those with high arterial stiffness (65.1%) to those with low arterial stiffness (53.7%)[36].

In the current study analysis, the study conducted by Hurst et al. (2015), the data presented indicated that the number of participants was more significant among individuals with T2DM who experienced the progression of microvascular complications leading to hypertension, in comparison to those with T2DM and non-microvascular complications. The analysis revealed that microvascular damage significantly contributes to developing high blood pressure in patients with T2DM. The forest plot indicates a higher likelihood of increased blood pressure in individuals with microvascular complications than those without it. The statistical significance of the analysis suggests a notable low in heterogeneity, thereby validating the appropriateness of conducting a meta-analysis.

The above analysis is supported by a study wherein they include individuals with hyperglycemia who experience microvascular complications, which exhibit an increased likelihood of developing hypertension.
compared to those with non-microvascular complications\cite{23,37}. In addition, a study wherein they performed an analysis on measurements of arterial stiffness. The findings indicated that diabetic patients aged 30 to 65 exhibited significantly higher systolic and pulse pressure values than non-diabetic individuals\cite{38}.

Furthermore, this study also discovered a substantial difference in HbA1c values between people with diabetes (65.4\%) and those without diabetes (40.4\%). Interestingly, this analysis is supported by a study that demonstrated that the participants with diabetic peripheral neuropathy with high HbA1C level was significant and increased three times from 6.9\% to 28.5\%\cite{39}.

Conclusion
In conclusion, the results obtained from this study demonstrate a significant positive correlation between hyperglycemia and elevated blood pressure levels among the adult demographic. The progression of elevated blood pressure in individuals with hyperglycemia is attributed to microvascular complications and arterial stiffness. Furthermore, there exists a strong correlation between both factors. The association between micro- and macrovascular complications in individuals diagnosed with T2DM has been observed to be linked to a subsequent increase in arterial stiffness. This increase in arterial stiffness, in turn, plays a role in the progression of hypertension. Moreover, the HbA1c biomarker is commonly used to detect changes in blood pressure in hyperglycemic individuals, owing to its relationship with problems or factors that can raise blood pressure.

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Conflict of Interest Disclosure
None to declare

References


