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Association Between HBA1C and Inflammatory Markers: HS-CRP and Homocysteine

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Abstract

Introduction: Hyperglycemia is the condition that if the body has high blood sugar levels, it results in the insulin resistance and inflammation within the body. It can increase the level of inflammatory markers suchas hs-CRP and homocysteine in the blood. Both hs-CRP and homocysteine are involved in inflammation within the body and also are associated with arteriosclerosis diseases such as coronary artery disease, stroke, and peripheral vascular disease.

Objectives: To study the association between HbA1C and inflammatory markers levels including hs-CRP and homocysteine.

Methods: About 90 cases, ages between 35 and 65 years were collected data from the Bangkok Anti-Aging Center's medical recording between July 2019 and March 2020. Independent variable was HbA1c and the dependent variables were hs-CRP and Homocysteine. Pearson's correlation coefficient was used to detect the correlations between HbA1c and hs-CRP and Homocysteine.

Results: HbA1c was positively correlated with hs-CRP in the blood with statistically significant ($r = 0.33$, $p = 0.001$) and HbA1C also was positively correlated with homocysteine with statistically significant ($r = 0.53$, $p < 0.001$). In addition, BMI was positively correlated with hs-CRP, and homocysteine with statistically significant $r = 0.33$, $p = 0.002$; 0.32, $p = 0.002$, respectively.

Conclusion: High levels of inflammatory markers were found not only in those diagnosed with diabetes but in those with HbA1C diagnosed with pre-diabetes which were found to have high inflammatory markers as well. Therefore, if we can control HbA1C to normal level (HbA1C < 5.7) without focusing only on people with diabetes but in people who are pre-diabetes by adjusting diet and exercise to keep HbA1C and weight to a normal level, it can help to reduce inflammation within the body and blood vessels and help to reduce arteriosclerosis in the future. This is an important and common complication in patients with hyperglycemia as well.

***Keywords*:** HbA1C, Hs-CRP, Homocysteine

Introduction

Inflammation is the leading factor in atherosclerosis and coronary artery disease by stimulating arterial thrombosis (Silva and de Lacerda, 2012). There are many inflammatory markers indicating that inflammation in the body, but high-sensitivity C-reactive protein (hs-CRP) is the best inflammatory marker indicating the risk of arteriosclerosis both in the prevention and treatment of disease (Koenig, 2013). CRP is generated from the liver after being stimulated by IL-6 and IL-1β when inflammation occurs. CRP can be measured in the range 10-1,000 mg/L but high-sensitivity C-reactive protein (hs-CRP) can be measured as low as 0.3 mg/L which is sensitive and correlated to coronary artery disease in the future. It is useful for assessing the risk of coronary heart disease (Ramesh *et al.*, 2019).

Homocysteine is a sulfur-containing amino acid. Homocysteine is a metabolite obtained from the process of demethylation of the amino acid methionine which is found primarily in animal protein. Homocysteine plays a role in the reaction of transmethylation of protein metabolism. There are several studies that have found that high homocysteine (Hyperhomocysteine) increases the risk of cardiovascular disease including premature coronary artery disease, stroke, and venous thromboembolism although the patient had normal lipid levels (Stampfer *et al.*, 1992). In addition, the abnormality of increased blood homocysteine (Hyperhomocysteine) levels was reported in those who had Insufficient intake of vitamin B6 (pyridoxine), B12 (cobalamin), and folic acid (Currò *et al.*, 2014).

HbA1c is a form of hemoglobin. HbA1c in the patient's blood can reflect the patient's control of diabetes over the past three months. Which is the mean age of red blood cells (Bonora and Tuomilehto, 2011). HbA1c is currently used in the diagnosis of diabetes according to the American Diabetes Association (ADA) guideline 2018 and the American Association of Clinical Endocrinologists. By interpreting the HbA1c as follows, HbA1c <5.7% means non-diabetes, HbA1c = 5.7 - 6.4% means that there is a risk of diabetes (Pre-diabetes) and HbA1c ≥ 6.5% means Diabetes.

High-sensitivity C-reactive protein (hs-CRP) levels were statistically positively correlated with HbA1c in people with poor sugar control. This is because hyperglycemia leads to inflammation. Glycation is the cause of the inflammatory process which leads to an increase in High-sensitivity C-reactive protein (hs-CRP) (Ahmed, 2018). Based on research by Amanullah *et al.* (2010) found that High-sensitivity C-reactive protein (hs-CRP) is high in people with insulin resistance with statistically significant ($p < 0.001$) and High-sensitivity C-reactive protein (hs-CRP) was found to be higher in people with diabetes than in non-diabetic people with statistically significant ($p < 0.001$). Correspond to the research of Ahmed (2018) which found a significant positive relationship between HbA1c and CRP in patients with coronary heart disease ($p = 0.001$). In addition, high HbA1c, high CRP, and diabetes were found to be statistically significant ($p < 0.05$). Research by Bansal *et al.* (2016) found that there was an increase in homocysteine in patients with Type 2 diabetes mellitus compared to the non-diabetic group with statistically significant. Correspond to the research by Drzewoski *et al.* (2000) which found that diabetic patients had an increase in homocysteine with statistically significant ($p <0.05$).

Since there is little information available about the study of HbA1c effects to inflammatory markers with vascular inflammation (high-sensitivity C-reactive protein (hs-CRP) and homocysteine) in Thailand. Thus, this study was conducted to study the effect of HbA1c with inflammatory markers: High-sensitivity C-reactive protein (hs-CRP) and homocysteine, for the benefit of patients with hyperglycemia to predict and prevent arteriosclerosis.

Materials and Methods

Study design

This analytical research aimed to study in two objectives, firstly the correlation between Hemoglobin A1C (HbA1C) and High-sensitivity C-reactive protein (hs-CRP) in the blood and also to study the correlation between Hemoglobin A1C (HbA1C) and Homocysteine in the blood.

Study participants

Ninety cases were collected data from the Bangkok Anti-Aging Center's medical records between July 2019 and March 2020. The inclusion criteria of the patients in the present study were patients who were 35 – 65 years. The exclusion criteria were patients who drank more than 2 alcoholic drinks per week, smoking, high-sensitivity C-reactive protein (hs-CRP) ≥ 10 mg/L, history of atherosclerosis disease such as coronary artery diseases, cerebrovascular disease (Stroke), and peripheral vascular disease.

Ethics

This study only used the number of patients instead of personal data, so this can ensure the confidential information.

Data collection

Selection of 90 cases, ages between 35 and 65 years, were collected data from the Bangkok Anti-Aging Center's medical records between July 2019 and March 2020 according to the inclusion criteria and exclusion criteria. Blood results were collected from the patient's medical record including blood glucose (HbA1C) data, inflammatory markers (high-sensitivity C-reactive protein (hs-CRP), and homocysteine), renal function (Creatinine), and liver function tests (AST, ALT). Basic patient information such as gender, age, BMI, and blood pressure were collected and were analyzed for further statistical outcome.

Statistical Analysis

The independent variable was HbA1c. The dependent variables were hs-CRP and homocysteine. Pearson's correlation coefficient was used to detect the correlations between HbA1c and hs-CRP and Homocysteine. Basic data were analyzed by using descriptive analysis.

Results and Discussion

According to the study, 90 patients were divided into 46 males and 44 females. The average age was 51.68(±8.75) years, with a minimum age of 35 and a maximum age of 65. The average weight was 67.62(±13.54) kg with a minimum weight of 40 kg and a maximum weight of 107 kg. The average height of 164.14(±7.13) cm with a minimum height of 148 cm and a maximum height of 180 cm (see Table 1).

Table 1: Demographic data

Parameters	n	Mean(±SD)	Min	Max
Sex				
Male	46			
Female	44			
Age (years)		51.68(±8.75)	35	65
Weight (Kg)		67.62(±13.54)	40	107
Height (Cm)		164.14(±7.13)	148	180
BMI (Kg/m^2)		24.94(±3.92)	16.6	35.8
SBP (mmHg)		127.36(±19.1)	93	185
DBP (mmHg)		81.16(±11.17)	60	110

The average of Aspartate aminotransferase (AST) was 24.4(±10.48) units per liter with the minimum and maximum values of 10 and 70 units per liter. The average of Alanine aminotransferase (ALT) was 29.28(±16.5) units per liter with the minimum and maximum values of 10 and 111 units per liter. The average of renal function (Creatinine) was 0.84(±0.24) mg/dL with the minimum and maximum values of 0.51 and 1.81 mg/dL (see Table 2).

Table 2: Liver function test (Aspartate aminotransferase (AST) and Alamine aminotransferase (ALT) and Renal function (Creatinine)

Parameters	Mean(±SD)	Min	Max
AST (U/L)	24.4(±10.48)	10	70
ALT (U/L)	29.28(±16.5)	10	111
Creatinine (mg/dL)	0.84(±0.24)	0.51	1.81

The average HbA1C was 6.44(+1.83) percent, with the minimum and maximum HbA1C of 4.1 and 13 percent. The average of high-sensitivity C-reactive protein (hs-CRP) was 2.6(+ 2.75) mg/L, with the minimum and maximum hs-CRP of 0.21 and 9.9 mg/L. The average of homocysteine was 10.26(+0.42) μmol/L with the minimum and maximum of 8.9 and 11.2 μmol/L (see Table 3).

Table 3: HbA1C, hs-CRP and homocysteine data

Parameters	Mean(+SD)	Min	Max
Hemoglobin A1C (%)	6.44(+1.83)	4.1	13
hs-CRP (mg/L)	2.6(+2.75)	0.21	9.9
Homocysteine (umol/L)	10.26(+0.42)	8.9	11.2

From this study, HbA1c was positively correlated with high-sensitivity C-reactive protein (hs-CRP) with statistically significant (r = 0.33, p = 0.001). This is consistent with previous study done by Amanullah *et al.* (2010) indicating that high-sensitivity C-reactive protein (hs-CRP) blood levels were significantly higher in people with diabetes than in non-diabetic people (p <0.001). In addition, HbA1C was positively correlated with high-sensitivity C-reactive protein (hs-CRP) with statistically significant (r = 0.307, p <0.001). Another study done by Ramesh *et al.* (2019) found that in type 2 diabetes patients, both HbA1C levels and high-sensitivity C-reactive protein (hs-CRP) were statistically related (p = 0.004) (see Table 4).

Table: 4 Pearson's Correlation between Hba1c and other risk variables in total subjects.

Parameters	r	*p*-value
Hs-CRP	0.33	0.001
Homocysteine	0.53	<0.001
BMI	0.34	0.001

HbA1c was also positively correlated with homocysteine with statistically significant (r = 0.53, p < 0.001). This is consistent with previous study done by Drzewoski *et al.* (2000) indicating that diabetic patients with poor glycemic control (Uncontrolled diabetes) had homocysteine levels significantly higher than controlled diabetes patients and the healthy control group with p < 0.001. It was also found that HbA1c was positively correlated with homocysteine in uncontrolled diabetes patients with statistically significant (r = 0.41; p < 0.05). In addition, previous study done by Bansal *et al.* (2016) found that HbA1c and homocysteine were significantly positively correlated (r = 0.416, p <0.05). In addition, the present study found that HbA1c was positively correlated with the body mass index (BMI) with statistically significant (r = 0.34, p = 0.001). This is consistent with previous study done by Amanullah *et al.* (2010) indicating that Body mass index (BMI) was significantly associated with HbA1c (p < 0.001). However, HbA1c was not significantly correlated with AST, ALT, and Creatinine.

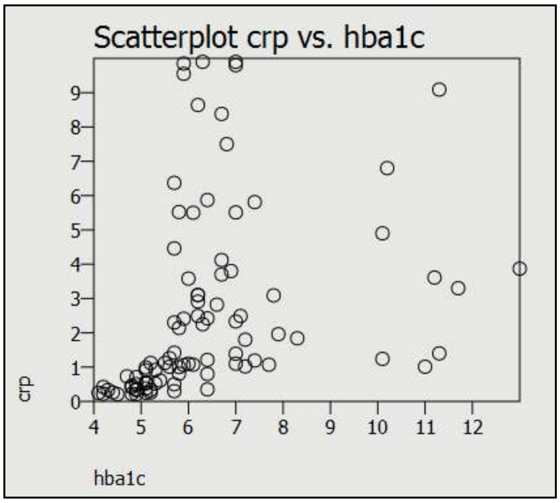

Figure 1: Showing positive correlation between HbA1c and High-sensitivity C-reactive protein (hs-

CRP) (r = 0.33, *p* = 0.001).

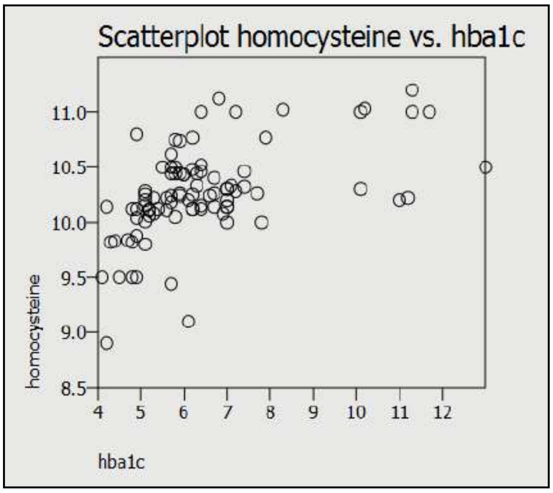

Figure 2: Showing positive correlation between HbA1c and Homocysteine (r = 0.53, *p* < 0.001).

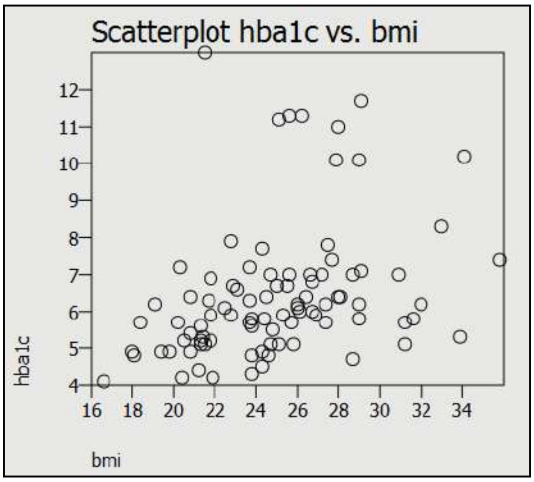

Figure 3: Showing positive correlation between HbA1c and body mass index (BMI) (r = 0.34, *p* = 0.001).

Finally, the body mass index (BMI) was positively correlated with high-sensitivity C-reactive protein (hs-CRP) with statistically significant (r = 0.33, *p* = 0.002). This is consistent with previous study done by Amanullah *et al.* (2010) indicating that body mass index (BMI) was positively correlated with high-sensitivity C-reactive protein (hs-CRP) with statistically significant (r = 0.238, *p* <0.001). In addition, the body mass index (BMI) was positively correlated with homocysteine with statistically significant (r = 0.32, *p* = 0.002). This is consistent with previous study done by Sachan *et al.* (2012) indicating that the body mass index (BMI) was associated with homocysteine levels (*p* <0.001) (see Table 5).

Table 5: Pearson's Correlation between body mass index (BMI) and other risk variables in total patients.

Parameters	r	*p*-value
Hs-CRP	0.33	0.002
Homocysteine	0.32	0.002

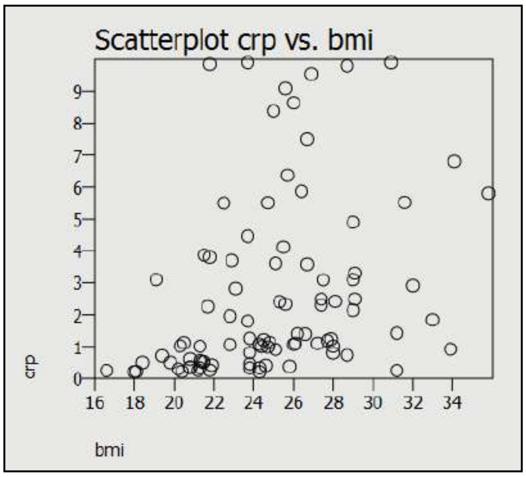

Figure 4 : Showing positive correlation between body mass index (BMI) and High-sensitivity C-reactive protein (hs-CRP) (r = 0.33, *p* = 0.002).

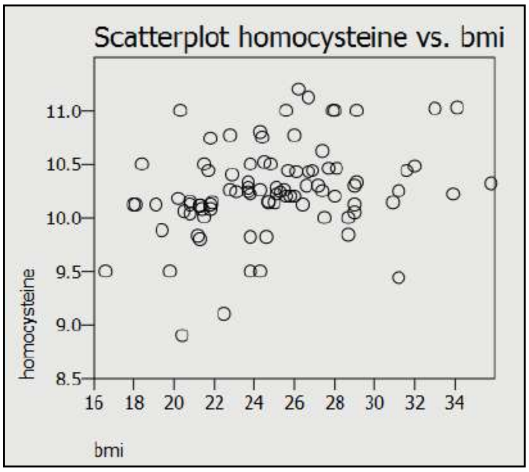

Figure 5: Showing positive correlation between body mass index (BMI) and Homocysteine (r = 0.32, p = 0.002).

Hyperglycemia is the condition that the body has high blood sugar levels results in the insulin resistance and inflammation within the body. It can increase the level of inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) and homocysteine in the blood. The high-sensitivity C-reactive protein (hs-CRP) and homocysteine are involved in inflammation within the body and also are associated with arteriosclerosis diseases such as coronary artery disease, stroke and peripheral vascular disease (Koenig, 2013). In the present study, HbA1c was positively correlated with inflammatory markers including hs-CRP and homocysteine with statistically significant r = 0.33, p = 0.001; r = 0.53, $p < 0.001$, respectively. In addition, BMI was positively correlated with hs-CRP, and homocysteine with statistically significant r = 0.33, p = 0.002; 0.32, p = 0.002, respectively. These inflammatory markers including high-sensitivity C-reactive protein (hs-CRP) and homocysteine, indicated the risk of arteriosclerosis which could lead to vascular disease in the future. The high levels of inflammatory markers was found not only in those diagnosed with diabetes, but also in those with HbA1c diagnosed with pre-diabetes (HbA1c 5.7-6.4) which were found to have high inflammatory markers. Therefore, if we can control HbA1c to normal level (HbA1c < 5.7) without focusing only on people with diabetes but in people who are pre-diabetes by adjusting diet and exercise to keep HbA1c and weight to normal level, it can help to reduce inflammation within the body and blood vessels and help reduce arteriosclerosis in the future which is an important and common complication in patients with hyperglycemia as well.

Conclusions

This study investigated the association between HbA1C and inflammatory markers levels including hs-CRP and homocysteine. HbA1c was positively correlated with hs-CRP and homocysteine. High levels of inflammatory markers were found not only in those diagnosed with diabetes but in those with HbA1C diagnosed with pre-diabetes. If we can control HbA1C to normal level, it can help reduce inflammation within the body and blood vessels and help reduce arteriosclerosis in the future.

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Contributors

H.K. originated the concept; collected data; conducted the research; designed the study; critically analyzed data; performed a literature search; drafted the manuscript. J.R. originated the concept; designed the study; interpreted the data; drafted the manuscript. P.S. designed the study; interpreted the data; critically revised the final version of the manuscript. H.K., J.R., and P.S. approved the final version. This research paper is a part of first author's (H.K.) Thesis in Anti-Aging and Regenerative Medicine, School of Anti-Aging and Regeneration Medicine, Mae Fah Luang University, Bangkok, Thailand.

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