The Effect of Diabetes Mellitus Control on Subclinical Inflammation in Type 2 Diabetes Mellitus

Walid Abd El Mohsen Shehab Eldin MD[1], Mohamed Zakarya Nouh MD[1], Azza Mohamed Kamel Abdallah MD[2], and Dina Abd El-Basset Shokr M.B., B.Ch[3].

[1] Department of Internal Medicine, Faculty of Medicine-Menoufia University, Egypt.
[2]Department of Biochemistry, Faculty of Medicine-Menoufia University. Egypt.
[3] Department of Internal Medicine, Ministry of Health, Egypt.
dinaabdelbaset33@gmail.com

Abstract: Purposeful: To study the state of subclinical inflammation in patients with type 2 diabetes mellitus. Moreover, to study the relation, if any, between glycemic control and inflammation. **Background:** Subclinical inflammation and presence of almost all indicators of systemic inflammation are found in type 2 diabetic patients. Such a systemic and subclinical inflammatory process can be characterized by elevated circulating levels of inflammatory markers. **Methods:** This research included 90 subjects divided into 2 groups; Group A: 70 patients with type 2 diabetes at the time of presentation and Group B: 20 Age and sex matched people as the control group. After providing written informed consent, all patients were clinically examined, had laboratory investigations including; fasting and 2 hours postprandial blood sugar, HbA1c, serum ferritin., high sensitivity C-reactive protein, kidney functions tests, liver function tests, complete blood count and erythrocyte sedimentation rate and antinuclear antibody. **Results:** Regarding laboratory investigations there was significant difference between the two group regarding revealed that diabetic patients had higher values of; ESR, Hs-CRP and serum frritin. Correlation study revealed significant positive correlation between HbA1c and (Hs-CRP and serum frritin). **Summary:** Our findings suggest that there is augmented inflammation in T2DM patients manifested by elevated ESR, serum ferrtin and hs-CRP. Also, we found significant positive correlation between HbA1c and (Hs-CRP and serum ferritin). All these finding suggesting a link between inflammation and glycemic control in patient with type 2 diabetes mellitus.
[Walid Abd El Mohsen Shehab Eldin, Mohamed Zakarya Nouh, Azza Mohamed Kamel Abdallah, and Dina Abd El-Basset Shokr. **The Effect of Diabetes Mellitus Control on Subclinical Inflammation in Type 2 Diabetes Mellitus.** *Stem Cell* 2017;8(2):121-125]. ISSN: 1945-4570 (print); ISSN: 1945-4732 (online). http://www.sciencepub.net/stem. 19. doi:10.7537/marsscj080217.19.

Key words: Diabetes mellitus, Subclinical inflammation.

1. Introduction

Type 2 diabetes (T2D) is a major global health problem affecting 415 million people (215 million of men and 199 million of women). It is considered that this number will rise to 642 million in 2040. Of these, 90-95% of cases are T2D (**1**).

Subclinical inflammation and presence of almost all indicators of systemic inflammation are found in type 2 diabetic patients. Such a systemic and subclinical inflammatory process can be characterized by elevated circulating levels of inflammatory cytokines including C-reactive protein (CRP) or high-sensitivity CRP (hs-CRP) (**2**).

High sensitivity C-reactive protein (hsCRP) is a C-reactive protein measured by a highly sensitive assay. CRP represents the classical acute-phase protein produced in the liver in response to inflammatory stimuli, and plasma levels of hsCRP provide a sensitive marker of increased inflammatory activity in the arterial wall (**3**).

Chronic, systemic subclinical inflammation has also been identified as a driving force for insulin resistance, metabolic syndrome, and type 2 DM. Some related metabolic disorders include abdominal adiposity, hypertension, endothelial dysfunction, and glucose intolerance, which often occur in a cluster. Insulin resistance correlates closely with the risk of cardiovascular diseases (CVD), explaining some of the excess morbidity and mortality in type 2 DM patients (**4**).

Because the development of complications is linked to the accumulation of glycation adducts in tissue proteins. The core of the issue is glycemic control. Optimal monitoring of glycemic control involves plasma glucose measurements (fasting and postprandial blood sugar) and measurement of glycated hemoglobin (HbA_1c). These measurements are complementary: the patient's glucose measurements provide a picture of short-term glycemic control, whereas HbA_1c reflects average glycemic control over the previous 3 months (**5**).

2. Methods:

Approval by a healthcare facility Ethics Panel, and written informed patient consent with justification about the purpose, methods, results, and difficulties were delivered to all enrolled subjects. This research included 90 subjects divided into 2 groups.

- **Group A:** 70 patients with type 2 diabetes at the time of presentation.
- **Group B:** 20 Age and sex matched people as the control group.

After providing written informed consent, all patients were clinically examined, had laboratory investigasions including; fasting and 2 hours postprandial blood sugar, HbA1c, serum ferritin., high sensitivity C-reactive protein, kidney functions tests, liver function tests, complete blood count and erythrocyte sedimentation rate and antinuclear antibody.

Record analysis

All data were collected, tabulated and statistically analyzed using SPSS (SPSS Inc., Chicago, IL, USA). Data were expressed as mean. Student's t-test was used to determine the big difference between the analyzed variables in the two teams. Mann–Whitney U test was used to assess the null hypothesis that it is equally likely that a randomly selected value from one sample will be less than or greater than a randomly selected value from a second sample. The frequencies were stated in %. Relationship coefcient (r) was used to judge the relation between the studied parameters in the same group. Possibility (P) was considered significant if lower than 0. 05 and highly signifcant if less than 0. 001**(6).**

3. Results

Comparability between the two analyzed groups according to demographic data revealed that there was no significant difference regarding age and sex.. (**Table 1**).

Regarding laboratory investigations there was significant difference between the two group regarding; ESR, FBS, PP blood sugar, Hs-CRP and serum frritin (**Table 2**).

Correlation study revealed significant positive correlation between HbA1c and (Hs-CRP and serum frritin) (**Figures 1 & 2**).

There were significant positive correlations between serum ferritin and the following (BMI, FBS and PPBS) (**Table 3**).

There were significant positive correlations between hs-CRP and the following (BMI, FBS and PPBS) (**Table 4**).

Table 1: Comparison between two groups regarding age and sex

		Non diabetic (n=20)	Diabetic (n=70)	**Test of sig.**	**p**
Age (years) Mean ± SD.		50.3+5.6	50.83±8.26	t-test= 0.331	0.742
Sex	**Male**	6	12	X^2= 0.904	0.342
	Female	14	58		

Table 2: Comparison between the two studied groups regarding laboratory investigation

	Not diabetic (n=20)	**Diabetic (n=70)**	**Unpaired (t) test**	**P value**
ESR (mm/h)	12.4 ± 3.41	10.69± 3.05	2.158	0.034*
FBS (mg/dL)	83.25±6.25	186.01±92.21	11.155	0.000*
P. PBS (mg/dL)	120.9±8.76	289.7±125.54	9.251	0.000*
HSCRP (ng/mL)	45.088±39.35	6005.2±3639.83	13.697	0.000*
Ferritin (ng/mL)	19.97±18.51	155.75±73.95	13.913	0.000*
HBA1C (%)	4.555±0.58	7.5±3.23	9.95	0.000*

*Significant

Table 3: Correlation and regression of Ferritin on other data

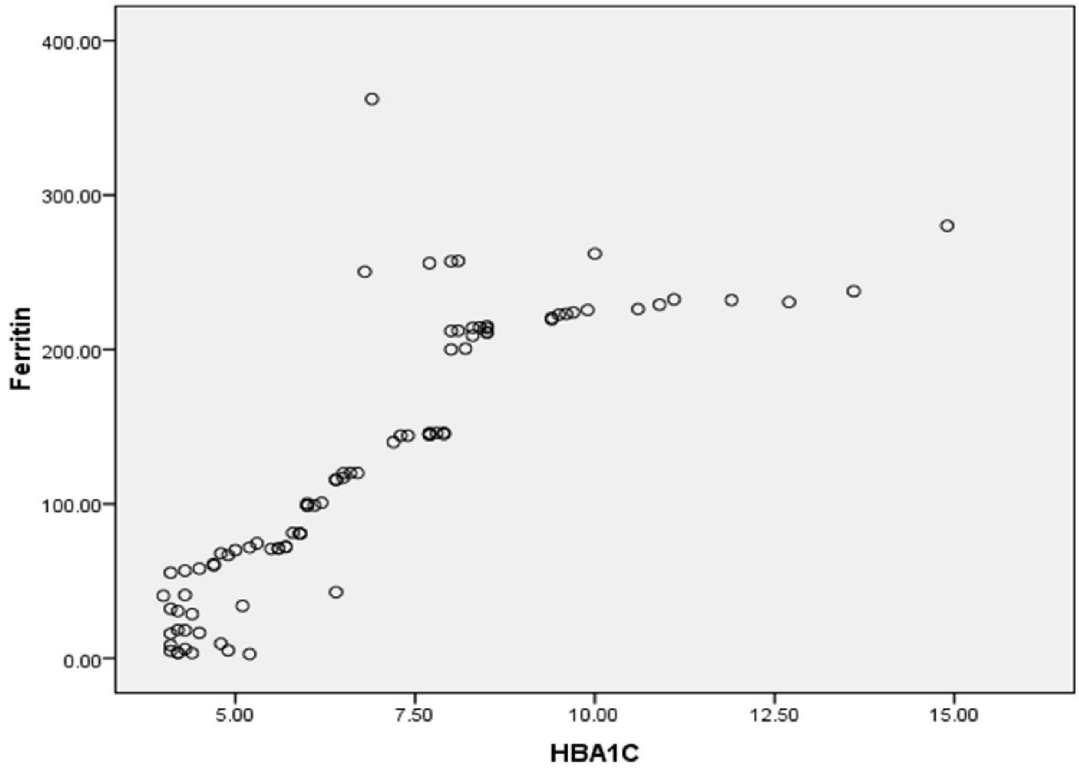
	R	**P value**
BMI	0.319	0.002*
FBS	0.352	0.001*
PPBS	0.484	0.000*

*Significant

Table 4: Correlation of HSCRP with other data

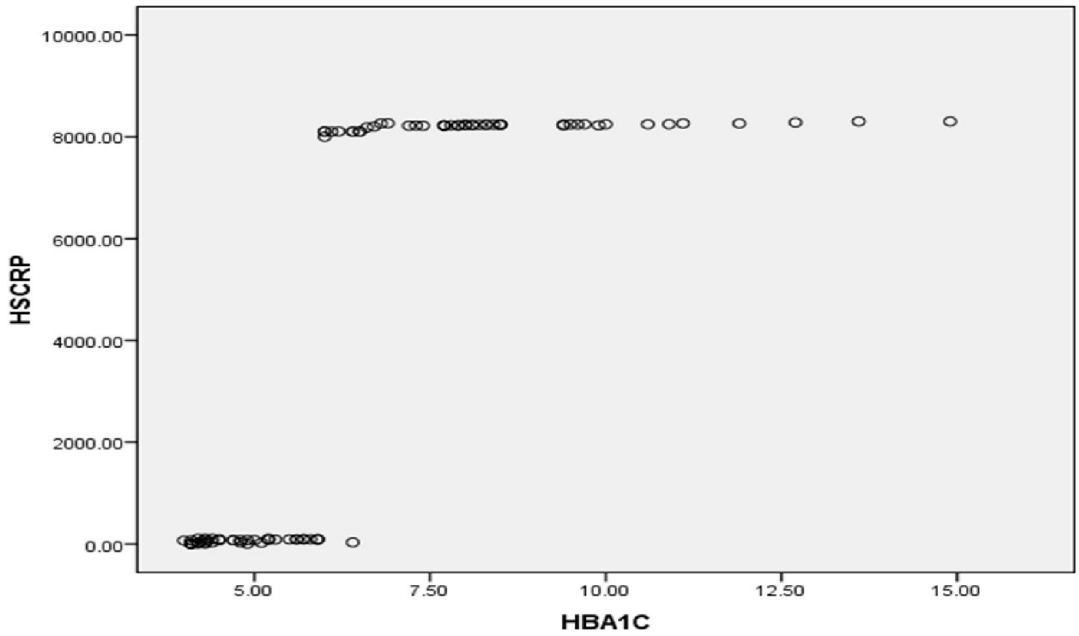
	R	**P value**
BMI	0.272	0.01*
FBS	0.288	0.006*
PPBS	0.417	0.000*

*Significant



(r= 0.853, p= 0.000*)

Figure 1: Correlations between HbA1c and serum ferritin



(r= 0.761, P value = 0.000*).

Figure 2: Correlations between HbA1c and hs-CRP.

4. Discussion

In the current study ESR level was significantly elevated in control group than diabetic patients. **Nadeem and her colleagues** found higher levels of ESR in diabetic patients than in healthy indicating the role of inflammation in pathogenesis of the disease. Inflammatory markers were not found to be higher with increasing age (**7**).

Regarding hs-CRP, it was significantly elevated in diabetic patients than healthy control. This findings are in accordance with the finding of study conducted to assess the level of hs-CRP in diabetic patients as they found that the levels of hsCRP was statistically higher in T2D patients compared to healthy population (**8**). However, this disagrees with the findings **Lima of and his colleagues** as they found no significant difference between patients with type 2 diabetes mellitus and healthy controls (**9**), this discrepancy in results may be explained as their results was illustrated in median values and our result were illustrated as mean ± SD.

Serum ferritin is an acute phase reactant, and is a marker of iron stores in the body (**10**).

In this regard we found that diabetic patients had significantly elevated level of serum ferritin than healthy individuals. This finding is supported by a prospective case control study conducted by **Kumar et al** as they reported that patients with T2DM had significantly higher serum ferritin level when compared to healthy controls. (**11**).

In the present study, there were significant positive correlations between HbA1c and HsCRP. This is in accordance with the findings **Sarinnapakorn et al.** as they found that hsCRP levels correlated with HbA1c levels. Mean HbA1c levels were significantly higher in patients who had hsCRP levels of 1 mg/L or more. Other factors such as age, blood pressure, BMI, LDL cholesterol, serum creatinine were not correlated with hsCRP level (**12**).

We found that serum ferritin is significantly associated with HbA1c, FBS and PP glucose. This is in accordance with the findings of recent study conducted by **Arora** which found that serum ferritin was proportional to blood glucose level (**13**). However, our finding disagrees with **Sharifi and Sazandeh** as they reported no correlation between serum ferritin with HbA1c in diabetics and normal controls (r=0.23), they supposed that the use of blood letting may affect total hemoglobin level and HbA1c as well, so the use of HbA1c as a marker of blood glucose control has not been appropriate (**14**).

Positive correlation between ferritin and HBA1c as well as FBS indicates hyperglycemia causing increased glycation of hemoglobin and increased release of free iron from glycated proteins like hemoglobin. This makes a vicious cycle of hyperglycemia, glycation of hemoglobin and increase in levels of free iron and ferritin. This increased presence of iron pool will enhance oxidant generation leading damage to biomolecules (**15**).

In the present study there was no correlation between serum ferritin and age (r=0.037, p-value=0.726). This is in accordance with the findings of **Fernedez and his colleagues** as they found no association between serum ferritin and age in diabetic patients (**16**). However, this is disagree with the findings of **Padmaja and his colleagues** as they found low significant positive correlation between serum ferritin and age in diabetic patients (**17**).

The elevated level of serum ferritin in our study can be explained as raised serum ferritin may possibly be related to the occurrence of long term complications of diabetes, both microvascular and macrovascular (**18**).

The present study declares that there is association between elevated glycated hemoglobin which reflect bad glycemic control and both of hs-CRP and serum ferritin which are inflammatory markers this reflect the role glycemic control and suclinical inflammation in patients with type 2 diabetes mellitus. In the line with our finding previous study suggested that elevated hs-CRP could be the expression of subclinical inflammation (**19**). Higher positive correlation of serum ferritin with HbA1c shows that hyperglycemia affects ferritin levels possibly due to inflammation or oxidative stress or a combination of the two (**17**).

Conclusion

Our findings suggest that there is augmented inflammation in T2DM patients manifested by elevated EDR, serum ferrtin and hs-CRP. Also, we found significant positive correlation between HbA1c and (Hs-CRP and serum ferritin). All these finding suggesting a link between inflammation and glycemic control in patient with type 2 diabetes mellitus..

References

1. Dall TM, Narayan KM, Gillespie KB, Gallo PD, Blanchard TD, Solcan M, O'Grady M, Quick WW. Detecting type 2 diabetes and prediabetes among asymptomatic adults in the United States: modeling American Diabetes Association versus US Preventive Services Task Force diabetes screening guidelines. Popul Health Metr 2014; 12:12.
2. Lee CC and Liu S. Role of Inflammatory Cytokines in Type 2 Diabetes. Review of endocrinology, 2008;19-21.

3. Pfützner A, Forst T: High-sensitivity C-reactive protein as cardio-vascular risk marker in patients with diabetes mellitus. Diabetes Technol Ther 2006,8(1):28–36.
4. Amanullah S, Jarari A, Govindan M: Mohamed Ismail Basha and Saira khatheeja: association of hsCRP with diabetic and non-diabetic individuals. Jordan J Biol Sci 2010,3(1):7–12.
5. Alvin C: Powers: diabetes mellitus. In Harrison's Principle of Internal Medicine. 16th edition. Edited by: et al, Kasper L. New York: McGraw-Hill; 2005:2152–2179.
6. Armitage P. Statistical methods in medical research. London: Blachwell Scientifc;1983.
7. Nadeem A, Naveed AK, Hussain MM, Raza SI. Correlation of inflammatory markers with type 2 Diabetes Mellitus in Pakistani patients. J Postgrad Med Inst 2013; 27(3):267-73.
8. Malenica M, Šilar M, Dujić T, Bego T, Semiz S, Škrbo S, Prnjavorac B, Čaušević A. Importance of inflammatory markers and IL-6 for diagnosis and follow up of patients with type 2 diabetes mellitus. Med Glas (Zenica) 2017; 14(2): 169-175.
9. Lima LM., Carvalho, Soares MdG, Sabino AL, Adriano de P., Fernandes AP., Bethâ NA., & Marinez SO.. (2007). High-sensitivity C-reactive protein in subjects with type 2 diabetes mellitus and/or high blood pressure. Arquivos Brasileiros de Endocrinologia & Metabologia, 51(6), 956-960.
10. Koorts AM, Viljoen M. Acute phase proteins: Ferritin and ferritin isoforms. University of Petoria, South Africa 2011; 154-84.
11. Kumar G T, Saravanan A, Ramachandran C and John Nitin Ashok. Mean blood glucose level and glycated haemoglobin level in patients of non-insulin dependent diabetes mellitus and its correlation with serum ferritin level. Int J Med Sci 2011; 4 (1 & 2): 13-17.
12. Sarinnapakorn V, Wanicagool W: Association between hs-CRP and Hba1c in overweight type 2 diabetic female patients. J Med Assoc Thai 2013, 96(3): S54–58.
13. Arora P. Correlation between Serum Ferritin and Glycated Hemoglobin Level in Patients of Type 2 Diabetes Mellitus. Int J Cur Res Rev 2017; 9(6):30-34.
14. Sharifi F and Sazandeh SH. Serum ferritin in type 2 diabetes mellitus and its relationship with HbA1c. Acta Medica Iranica, 42 (2): 142-145; 2004.
15. Jeevan K. Shetty, Mungli Prakash, Mohammad S. Ibrahim. Relationship between free iron and glycated hemoglobin in uncontrolled type 2 diabetes patients associated with complications. Indian J Clin Biochem. 2008;23(1):67-70.
16. Fernandez-Real JM, Richard- Engel W, Arroyo E, Balanca R, Casamitjana-Abella R. Serum ferritin as a component of the insulin resistance syndrome. Diabetes Care 1998; 21(1): 62-68.
17. Padmaja P, Shabana S, Shariq MAS. Serum ferritin and HbA1c levels in type 2 diabetes mellitus. Int J Clin and Biomed Res 2015; 1 (3):30-37.
18. Eshed I, Elis A, Lishner M. Plasma ferritin and type 2 diabetes mellitus. Endocr Res 2001; 27: 91-7.
19. Gohe MG and Chacko AN. Serum GGT activity and hsCRP level in patients with type 2 diabetes mellitus with good and poor glycemic control: An evidence linking oxidative stress, inflammation and glycemic control. Journal of Diabetes & Metabolic Disorders 2013, 12:56.

6/25/2017