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Contribution of High Sensible C-Reactive Protein (hsCRP) in the Assessment of the Risk of Onset of Type 2 Diabetes and Its Cardiovascular Complications

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Abstract

Background: Type 2 diabetes is a metabolic disease characterized by chronic hyperglycemia. The latter plays an essential role in inflammation by stimulating the production of pro-inflammatory cytokines or by increasing their secretion by an oxidative mechanism. These cytokines control the hepatic synthesis of an inflammatory protein called C-Reactive Protein (CRP). High or average values of CRP would have a predictive value of cardiovascular diseases and type 2 diabetes. The relationship between low CRP values and the risk of developing type 2 diabetes and its cardiovascular complications is not sufficiently studied. The hsCRP could serve as a predictive biomarker of risk of onset, follow-up and prognosis for type 2 diabetes and its cardiovascular complications. To answer this problem, we conducted this study, the aim of which was to study the predictive role of hsCRP in the risk of occurrence of type 2 diabetes and its cardiovascular complications. **Materials and Methods:** This is a prospective and cross-sectional case-control study involving 200 participants including 100 control women and 100 women with type 2 diabetes (mean age was respectively 49.89 years ± 8.26 & 51.92 years ± 7.18; p =

0.066). The interviews were conducted on the basis of a questionnaire. Physical examination collected biometric data and cardiovascular constants. The biochemical parameters such as hsCRP were analyzed by an automated Abbott device. **Results:** We noted that hsCRP was significantly higher in type 2 diabetic subjects compared to control subjects ($p < 0.0001$). In control women, we found a positive correlation between hsCRP and body mass index (rho = 0.40, $p < 0.0001$), waist-hip ratio (rho = 0.24, $p < 0.0001$), systolic blood pressure (rho = 0.30, $p = 0.003$), diastolic blood pressure (rho = 0.28, $p = 0.006$), total body fat (rho = 0.48, $p < 0.0001$), visceral fat level (rho = 0.47, $p < 0.0001$). At the same time, it was positively correlated with glycated hemoglobin (rho = 0.29, $p = 0.003$), fasting insulin (rho = 0.22, $p = 0.026$), HOMA-IR (rho = 0.21, $p = 0.034$), C-peptide level (rho = 0.35, $p = 0.0003$), total cholesterol (rho = 0.24, $p = 0.016$), HDL cholesterol (rho = 0.24, $p = 0.019$), apolipoprotein B (rho = 0.25, $p = 0.013$). At the same time, hsCRP was negatively correlated with adiponectin level (rho = -0.21, $p = 0.04$) and the nitric oxide level (rho = −0.26, $p = 0.01$). In contrast, in women with type 2 diabetes, hsCRP was positively associated with body mass index (rho = 0.38, $p = 0.007$), waist-to-hip ratio (rho = 0.43, $p = 0.002$), total body fat (rho = 0.25, $p = 0.014$), cardiac frequency (rho = 0.34, $p = 0.001$) and glycated hemoglobin (rho = 0.21, $p = 0.036$). **Conclusion:** hsCRP has a prognostic value in the evaluation of cardiovascular risk. It seems to play an important role in the pathogenesis of type 2 diabetes mellitus and its cardiovascular complications. It could thus be considered as a biomarker for the screening, monitoring and prognosis of type 2 diabetes mellitus.

Keywords

hsCRP, Biomarker, Inflammation, Type 2 Diabetes

1. Introduction

Diabetes mellitus (DM) is a chronic non-communicable disease [1], formed in the vast majority of cases (95%) with type 2 diabetes mellitus (T2DM) which mainly affects adults [2]. T2DM is a major public health problem. It is a costly pathology due to its chronicity and the severity of its complications [3] [4]. It is a metabolic disease characterized by chronic hyperglycemia and a low grade inflammatory state. Inflammation seems to play an important role in the pathogenesis of type 2 diabetes mellitus and its cardiovascular complications. In addition, chronic hyperglycemia plays an essential role in the initiation and progression of the inflammation reaction by stimulating the production of pro-inflammatory cytokines by monocytes [5].

Chronic hyperglycemia can also act through an oxidative mechanism by increasing the secretion of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) which control the hepatic synthesis of an inflammatory protein called C-Reactive Protein (CRP) [5]. CRP is a member of the pentraxin family of proteins. It is an acute phase reactant synthesized mainly by the liver. Serum CRP levels are elevated in response to inflammatory conditions. It has recently been reported that the presence of an inflammatory state reflected in even moderate

elevations of CRP values represents a predictive factor for the development of type 2 diabetes mellitus [6] [7]. In addition, CRP has a prognostic value in the evaluation of cardiovascular risk. The evaluation of extremely low concentrations of CRP is possible, this is the ultrasensitive CRP (hsCRP). Thus, CRP could be considered as a biomarker of risk of onset, follow-up and prognosis for type 2 diabetes mellitus. For a better understanding of this problem, we conducted this study, the aim of which was to study the predictive role of CRP in the risk of occurrence of type 2 diabetes and vascular dysfunction.

2. Materials and Methods

2.1. Study Participants and Protocol

This case-control study was conducted in Senegal on female subjects. A total of 200 subjects were included. We enrolled 100 healthy control females and 100 type 2 diabetic females. Subjects were recruited from the medical physiology laboratory of the University of Cheikh Anta DIOP (UCAD) in Dakar, Senegal.

For the inclusion criteria, the older age should be at least 18 years old, and having not taken lipid-regulating drugs before or having stopped taking the drug for at least three months. On the other hand, the subjects who observed an antihypertensive treatment had just stopped taking their treatment the day before the day of the survey. We recruited known and followed type 2 diabetic subjects. However, diabetes status was confirmed using a pre-established questionnaire followed by clinical examinations, and tests on fasting blood glucose and glycosylated hemoglobin. All subjects in the control group were individuals free of diseases especially hyperglycemia. Extreme care was taken to exclude diseases that were determined by medical history, clinical and biological examinations. The no inclusion criteria were pregnancy and lactation and the presence of another pathologies such as coronary artery disease, chronic liver pathology, and chronic kidney pathology.

All procedures were conducted in accordance with the standards of the Declaration of Helsinki. It was reviewed and approved by the Ethics Committee of UCAD (Reference: Protocole 027512018/CERruCAD). All study participants provided signed informed consent.

2.2. Anthropometric and Biologic Measurements

At recruitment, all the subjects underwent an interview through questionnaires including demographic characteristics and medical histories (age, history of hypertension, duration of diabetes mellitus, use of lipid-lowering medications, anti-diabetes medications, and antihypertensive medications). Clinical examination and biometric measurements (weight, height, waist size, hip size, body mass index, waist-to-hip ratio, global body fat, visceral fat level, and blood pressures) were collected from each subject. The biological samples have been taken the same day in the biochemistry laboratory in the FMPOS of UCAD.

The fasting venous blood was collected from all the participants after a 12

hours overnight fast. After serum and plasma were aliquoted and frozen at −20˚C for further analysis of blood parameters. By an automated Abbott device and reagents of the same brand, we determine the concentrations of total cholesterol, high-density lipoprotein cholesterol (HDL cholesterol), triglycerides, fasting blood glucose, glycosylated hemoglobin (HbA_1c), C-peptid.

Low-density lipoprotein cholesterol (LDL cholesterol) level was calculated by the Friedewald formula: LDL cholesterol = Total cholesterol − HDL cholesterol − Triglycerides/5.

Insulin was determined by Human Insulin ELISA kits (Human Insulin ELISA Kit #A05322.96 wells, Version 0118, Bertin Bioreagent, France). Insulin resistance was determined by the Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) using the following Matthews formula: HOMA-IR = (fasting insulin (mU/L) × fasting glucose (mMol)/L))/22.5.

hsCRP was measured using the immunoturbidimetric test. It is a quantitative immunoprecipitation method in liquid medium characterized by its speed of execution and the possibility of automation. Laboratories prefer this technique because of its low cost as well as the possibility of its automation on a standard analyzer. The precision of the technique is satisfactory.

Latex particles coated with human anti-CRP antibodies agglutinate when mixed with samples containing CRP. Agglutination causes a variation in absorbance that depends on the CRP content in the patient sample. The values of interest are then different from those of CRP. The usual values of hsCRP range from 0.10 to 5.00 mg/L. The correlations between hsCRP and cardiovascular risk.

A threshold < 3.00 mg/L was retained as a cardiovascular risk factor. However, the assessment of cardiovascular risk depends on the values of high sensible C-Reactive Protein (hsCRP).

Cardiovascular risk	None	Low	High	Very high
hsCRP level (mg/L)	<1.00	1.00 - 3.00	3.00 - 6.00	>6.00

2.3. Statistical Analysis

The data was entered using Excel version 2016 software. SPSS statistical software version 23.5 (IBM Corp., Armonk, NY, USA) was used for data analysis. The normality test of the distribution of variables was carried out on the basis of the Kolmogorov-Smirnov test. The descriptive study was expressed as means ± standard deviations (SD), as medians and quartile (Q) ranges and as percentages (%). The comparison of the means was carried out by Student's t test for the quantitative variables which follow a normal distribution. That of the medians was carried out by Mann Whitney's U test for the quantitative variables whose distribution does not follow the normal distribution. Strength of association between hsCRP and the different clinical and biochemical variables was estimated using the Spearman correlation test.

A p-value ≤ 0.05 was considered as significant in statistical analysis.

3. Results

3.1. Demographic Characteristics

The mean age for the control subjects and the type 2 diabetic subjects was respectively 49.89 years ± 8.26 & 51.92 years ± 7.18. The comparison of the means ages between the control and the type 2 diabetic was not significantly different (p = 0.066). The control subject age was between 35 and 72 years old while that of the diabetic subjects was between 20 and 67 years old.

3.2. Comparison of the hsCRP between the Different Group

The hsCRP mean for the control subjects group was 6.23 mg/L ± 6.57 and the hsCRP mean for the type 2 diabetic group was 9.24 mg/L ± 10.33. The difference of the hsCRP medians was statistically significant between control and type 2 diabetic groups, see Figure 1.

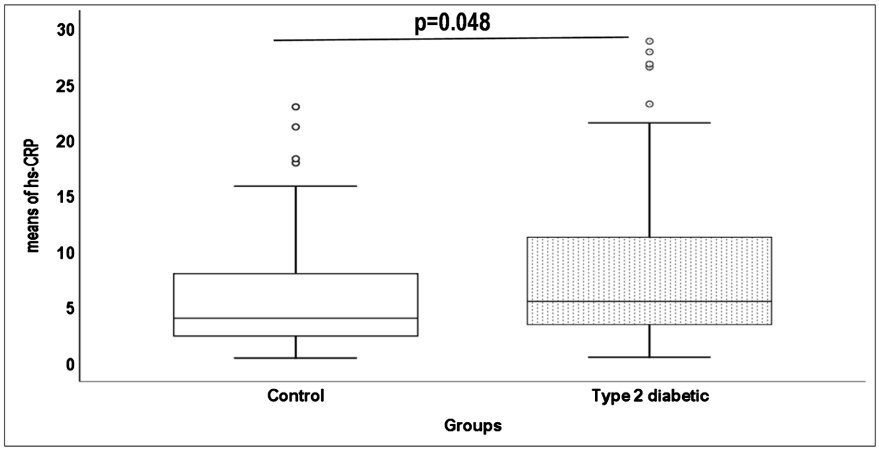

Figure 1. Comparaison of the hsCRP between the different groups. The hsCRP level was significantly higher in diabetic subjects compared to control subjects.

3.3. Biometric and Cardiovascular Characteristics

Type 2 diabetic subjects are statistically different from control subjects on the biometric level (WHR), on the cardiac level (heart rate). Indeed, type 2 diabetic subjects have a higher waist hip ratio and a faster heart rate, see Table 1.

Table 1. Comparison of biometric and cardiovascular parameters between study groups.

Variables	Control $n = 100$	Type 2 diabetes $n = 100$	*p*-value
Body mass index*			
Mean ± SD	29.26 ± 6.26	28.32 ± 5.35	0.253
Median (Q1 - Q3)	28.50 (24.80 - 33.40)	26.80 (24.73 - 31.88)	-
Waist hip ratio			
Mean ± SD	0.85 ± 0.08	0.89 ± 0.07	-
Median (Q1 - Q3)	0.85 (0.80 - 0.90)	0.89 (0.83 - 0.94)	0.007

Continued			
Total body fat*			
Mean ± SD	41.53 ± 6.92	40.10 ± 6.55	0.137
Median (Q1 - Q3)	42.60 (38.35 - 46.80)	40.55 (35.53 - 45.18)	-
Visceral fat level*			
Mean ± SD	9.15 ± 3.08	8.83 ± 2.96	0.461
Median (Q1 - Q3)	9 (7 - 11)	8 (7 - 10)	-
Adiponectin			
Mean ± SD	5.12 ± 3.17	5.17 ± 3.63	-
Median (Q1 - Q3)	4.35 (2.98 - 6.72)	4.33 (2.72 - 6.53)	0.890
Systolic blood pressure			
Mean ± SD	133.76 ± 23.87	138.74 ± 29.96	-
Median (Q1 - Q3)	134 (118 - 147)	132 (118 - 152)	0.436
Diastolic blood pressure*			
Mean ± SD	88.59 ± 15.27	89.34 ± 14.57	0.722
Median (Q1 - Q3)	88 (78 - 98)	87.50 (79.25 - 97.00)	-
Heart rate*			
Mean ± SD	75.94 ± 11.19	83.74 ± 12.50	<0.0001
Median (Q1 - Q3)	75.50 (68.00 - 83.25)	83.00 (76 - 90.75)	-
Oxide nitric			
Mean ± SD	743.86 ± 259.47	763.79 ± 226.47	-
Median (Q1 - Q3)	775.09 (531.74 - 940.90)	831.51 (605.53 - 923.56)	0.396

*: Normal distribution parameters for which Student's t test was applied.

3.4. Glycemic and Lipid Characteristics

Type 2 diabetic subjects are statistically different from control subjects in relation to the state of glycemic balance (fasting glucose and glycated hemoglobin), the resistance to insulin action (IR-HOMA, TG/HDL-c). In fact, diabetic subjects have significantly higher glycemic values and a very high resistance to insulin action compared to control subjects, see Table 2.

Table 2. Comparison of carbohydrate and lipid parameters between study groups.

Variables	Control $n = 100$	Type 2 diabetes $n = 100$	p-value
Fasting glucose			
Mean ± SD	0.84 ± 0.13	1.75 ± 0.89	-
Median (Q1 - Q3)	0.83 (0.77 - 0.92)	1.55 (1.05 - 2.30)	<0.0001
Glycated hemoglobin			
Mean ± SD	5.23 ± 0.59	8.87 ± 2.26	<0.0001
Median (Q1 - Q3)	5 (5 - 5.68)	8.60 (7.10 - 10.75)	-

Continued

C-Peptid			
Mean ± SD	1.21 ± 0.91	1.03 ± 0.56	0.085
Median (Q1 - Q3)	1.05 (0.58 - 1.56)	0.91 (0.63 - 1.46)	-
HOMA-IR			
Mean ± SD	2.17 ± 2.19	6.60 ± 11.91	-
Median (Q1 - Q3)	1.66 (1.02 - 2.64)	3.63 (2.12 - 6.58)	<0.0001
Triglycerides			
Mean ± SD	0.76 ± 0.32	0.95 ± 0.50	-
Median (Q1 - Q3)	0.76 (0.53 - 0.94)	0.80 (0.59 - 1.24)	0.572
TG/HDL-C			
Mean ± SD	1.39 ± 0.68	1.90 ± 1.32	-
Median (Q1 - Q3)	1.19 (0.88 - 1.63)	1.47 (0.97 - 2.45)	0.048
ApoA			
Mean ± SD	1.65 ± 0.34	1.67 ± 0.35	0.679
Median (Q1 - Q3)	1.62 (1.43 - 1.85)	1.68 (1.49 - 1.84)	-
ApoB			
Mean ± SD	1.07 ± 0.36	1.17 ± 0.37	0.068
Median (Q1 - Q3)	1.09 (0.81 - 1.24)	1.14 (0.91 - 1.41)	-
ApoB/ApoA			
Mean ± SD	0.66 ± 0.22	0.72 ± 0.25	-
Median (Q1 - Q3)	0.62 (0.50 - 0.76)	0.70 (0.55 - 0.90)	0.090

HOMA-IR: Homeostasis Model Assessment-Insulin Resistance, TG/HDL-C: Triglycerides/HDL cholesterol, ApoA: apolipoprotein A, ApoB: apolipoprotein B. *: normal distribution parameters for which Student's t test was applied.

3.5. Association between hsCRP and the Clinical and the Biochemical Parameters

In the control subjects group

In Table 3, we found that hsCRP was positively correlated with indices of obesity (body mass index, waist hip ratio, total body fat), with cardiovascular parameters (blood pressures, oxide nitric), with carbohydrate metabolism parameters (glycated hemoglobin, C-peptid, insulin resistance index (HOMA-IR)), and with lipid metabolism parameters (Total cholesterol, HDL cholesterol, apolipoprotein B).

Table 3. Relationships between hs-CRP and clinical and biochemical parameters in the control group.

Variables	Correlationships	
	Rho	*p-value*
Body mass index	0.40	<0.0001
Waist hip ratio	0.24	0.017

Continued

Total body fat	0.48	<0.0001
Adiponectin	−0.21	0.037
Systolic blood pressure	0.30	0.003
Diastolic blood pressure	0.28	0.006
Oxide nitric	−0.26	0.010
Glycated hemoglobin	0.29	0.003
C-peptid	0.35	0.0003
HOMA-IR	0.21	0.034
Total cholesterol	0.24	0.016
HDL cholesterol	0.24	0.019
Apolipoprotein B	0.25	0.013

HOMA-IR: Homeostasis Model Assessment-Insulin Resistance.

In the type 2 diabetic subjects group

In the type 2 diabetic group, we found that hsCRP was positively correlated with indices of obesity (body mass index, waist hip ratio, total body fat), with heart rate and glycated hemoglobin, C-peptid, insulin resistance index (HOMA-IR)), and with lipid metabolism parameters (total cholesterol, HDL cholesterol, apolipoprotein B), see Table 4.

Table 4. Comparison of carbohydrate and lipid parameters between study groups.

Variables	Correlationships	
	Rho	*p-value*
Body mass index	0.38	0.007
Waist hip ratio	0.43	0.002
Total body fat	0.25	0.014
Heart rate	0.34	0.001
Glycated hemoglobin	0.21	0.036

4. Discussion

Type 2 diabetes mellitus is a real public health problem due to its galloping prevalence and worrying incidence. It is characterized by heavy morbidity and mortality, the main source of which would be linked to its cardiovascular complications. The involvement of an inflammatory state in the physio-pathogenesis of type 2 diabetes mellitus and its cardiovascular complications has been widely reported [8]. The establishment of biological inflammatory factors predictive of the risk of onset of type 2 diabetes mellitus and its cardiovascular complications would be of decisive contribution in the monitoring and prognosis of these pathologies.

In this study, we found that the hsCRP level was significantly higher in type 2

diabetic subjects compared to control subjects. On the other hand, type 2 diabetic subjects were more prone to abdominal obesity and high heart rate. The results obtained are similar in the two study groups (control subjects and type 2 diabetic subjects).

We constated that hsCRP was positively correlated with indices of obesity (body mass index, waist hip ratio, total body fat). These results suggest a clear association between obesity and inflammation. This corroborates the literature data, obesity induces inflammation. In fact, high concentrations of free fatty acids from visceral fat enrich the liver and stimulate the synthesis of VLDL by hepatocytes. Elevated VLDL may lower HDL cholesterol levels by increasing the exchanges of HDL towards VLDL by the cholesterol transfer protein esterase. Adipose tissue can then synthesize cytokines such as TNF*α* and IL-6 [9].

We found that hsCRP was positively correlated with parameters of carbohydrate metabolism (glycated hemoglobin, C-peptid, insulin resistance index (HOMA-IR)). In effect, the first publication, concerning the role of inflammation in the pathogenesis of insulin resistance, is that of Hotamisligil GS. *et al.*, reporting an increase in the production of cytokines such as TNF*α* and IL6 by adipose tissue in the obese and improved insulin sensitivity during treatment with TNFα antagonists [10]. Mahajan *et al.* had shown in a study that hsCRP was an independent predictor of type 2 diabetes [11]. In another study, the authors found that hsCRP was independently associated with obesity, metabolic syndrome, impaired fasting blood sugar, glucose intolerance and resistance to insulin action [12]. In addition, the production of CRPus on the occasion of a cardiovascular condition is all the more important when the subject is diabetic [13].

It appears from the results that hsCRP was positively correlated with lipid metabolism parameters (Total cholesterol, HDL cholesterol, Apolipoprotein B). The close correlation between CRP concentrations and lipidemia is widely reported in the literature [14] [15]. hsCRP impairs macrophage uptake of LDL cholesterol [16], and thus increases serum LDL cholesterol levels.

We found that hsCRP was positively correlated with cardiovascular constants and parameters (blood pressures, oxide nitric). This finding suggests that hsCRP contribute to the pathophysiology of arterial hypertension and of atherosclerosis. Like the results of Torzewski M. *et al.* CRP is directly involved in the pathophysiology of arterial hypertension and of atherosclerosis [17]. Significant correlations have been reported between CRP concentrations and the onset of cardiovascular pathologies such as high blood pressure and atherosclerosis in healthy individuals [18].

A recent study demonstrates that CRP exerts a deleterious effect on the survival, differentiation and function of endothelial cell progenitor cells, resulting in negative effects on vessel repair and neovascularization of ischemic tissues [19]. On the other hand, CRP inhibits endothelial function to participate in angiogenesis [19]. In addition, the CRP level can predict the acute complications of atherosclerosis such as ischemic stroke, coronary artery disease [18] [20] [21].

Moreover, inflammation could provide a pathophysiological link between ath-

erosclerosis and one of its main risk factors, hypertension. Angiotensin II can lead to inflammation of the intima by induction of superoxide anion production from arterial endothelial cells and smooth muscle cells [22], and also by increasing the expression in smooth muscle cells of pro-inflammatory cytokines such as IL-6. Some authors suggest that cardiovascular risk factors such as obesity, diabetes mellitus, arterial hypertension and atherosclerosis induce lesions recognized by the body as danger signals [23] which would activate the innate and acquired immune system [24], leading to an inflammatory response. The diabetogenesis and atherogenesis of inflammation hypothesis explains the interest in characterizing new inflammatory markers that allow, independently of classic risk factors. Such innovations would make it possible to detect patients at high risk of developing type 2 diabetes and/or its cardiovascular complications.

hsCRP has been shown to be an independent predictor of various endpoints ranging from obesity, type 2 diabetes mellitus, metabolic syndrome, increased arterial intima-media thickness, and recurrent cardiovascular events. Additionally, large studies have primarily assessed the association of hsCRP and risk factors for cardiometabolic disease.

Obesity induces inflammation, predisposes to insulin resistance and diabetes, promotes atherogenic dyslipidemia, and potentiates atherogenesis. Given the close association between obesity and the risk of developing a low grade inflammatory state, the essential role of inflammatory mediators in diabetogenesis and atherogenesis and the involvement of inflammation in the pathophysiology of atherosclerotic plaque vulnerability, circulating markers of inflammation could also be biomarkers of obesity, type 2 diabetes, arterial hypertension and subclinical atherosclerosis. Thus, attention could focus on plasma concentrations of inflammatory biomarkers and their ability to predict an increased risk of developing cardiometabolic disease. The CRP is a circulating biomarker of inflammation. It has ideal characteristics to be a biomarker of risk [25]. The link of these circulating levels to a large number of cardiovascular risk factors such as obesity, dyslipidemia, resistance to the action of insulin, type 2 diabetes, arterial hypertension both in both children and adults has been widely demonstrated [26] [27] [28] [29] [30] [31]. The hsCRP assay can detect low CRP concentrations below 0.1 mg/L [32]. Its dosage in the laboratory can be done using rapid, low cost techniques with the possibility of using a standard analyzer. Thus, the use in clinical practice of the hsCRP assay to estimate the cardiometabolic risk seems more interesting than that of most of the biomarkers of inflammation.

The predictive capacities of plasma levels of hsCRP could be added to those of plasma lipid concentrations can provide a powerful prediction tool for a better management, especially preventive, of subjects at risk.

Another emerging feature of CRP-related biology is the local production of the CRP in the arterial wall. Studies indicate that smooth muscle cells are one of the most important sources of pro-inflammatory cytokines. The combination of pro-inflammatory cytokines IL-1β and IL-6 stimulate the production of CRP in

cells smooth muscle, which could be the origin of the local development of inflammation, proliferation and migration of smooth muscle cells in the subendothelial space.

5. Conclusion

Among recent paradigms concerning the development of type 2 diabetes, inflammation seems to play a major role in the initiation, progression and occurrence of cardiovascular complications. CRP, a circulating marker of inflammation, is closely associated with risk factors for cardio-metabolic diseases. It would be both a risk marker and a mediator of cardiometabolic disease. hsCRP is very sensitive and can detect low levels of CRP. Thus, hsCRP could be used to predict the risk of cardio-metabolic diseases in subjects at risk, should be taken into account as a simple and relevant prognostic element, but also as a therapeutic decision parameter. However, this point deserves further work on a larger scale.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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