Ministry of High Education
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Correlation of C-Reactive Protein (CRP) and Bacterial Infections with Diabetic Mellitus in Human

A project submitted to the council of the college of pharmacy in partial fulfilment of requirement for the degree of bachelors of pharmacy B.P.S

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بسم الله الرحمن الرحيم

(وقُل رَّبِّ زِدْنِي عِلْمًا)

صدق الله العظيم

Dedicated to,

Our parents who taught us to believe in ourselves, our teachers who used to lead light, to our Al-hashd and army men who spread peace, and finally, to our supervisor who helped us along the project work time.

Abstract:

Diabetes has been recognized as an important risk factor for a variety of intracellular bacterial infections, in this research, fifty five samples collected from patients with Diabetic Mellitus (DM), in Diabetic Mellitus Consulting Center in Marjan Teaching Hospital / Babylon Province for two months starting from November 2022, multiple clinical data of DM patients collected according to data sheet such as DM initiation date, family history of chronic diseases, active bacterial infections, and some others,control group including fifteen apparently healthy subjects, C-Reactive Protein (CRP) had been measured for all patients. Conclusion: The convergence of intracellular bacterial infections and diabetes poses new challenges for immunologists, providing the impetus for multidisciplinary research, in addition , detection of CRP values (besides other important immunological biomarkers) continuously in DM patients may be valuable biomarker and indication for other problems including cancer, osteoporosis, cardiovascular diseases , detection of sepsis in early stages and others.

Introduction :

Diabetic mellitus

History of Diabetic Mellitus

In 1869, Paul Langerhans, then aged 22 and working on his medical doctorate, identified the cells that came to be known as the ‘islets of Langerhans . However, the name insulin for the secretions of the islets (Latin, insula = island), which could bring down blood glucose levels, was coined only in 1909 and 1910, individually by de Mayer and Schaefer, respectively. In 1889, von Mering and Minkowski, when experimenting on dogs, found that removal of the pancreas led to diabetes. In 1921, Banting, Best and Collip, working in Macleod’s laboratory, ligated the pancreatic duct, causing the destruction of the exocrine pancreas while leaving the islets intact. In their elegant animal experiments, by using canine insulin extracts to reverse induced diabetes, they conclusively established that the deficiency of insulin was the cause of diabetic[1].

Previous diagnosis for diabetic mellitus Willis, a London physician, epitomized the true spirit of scientific enquiry by his bold action of tasting the urine of his patients—possibly because the passage of copious urine seemed to be the hallmark of the disease! This was a supreme and extreme example of bedside testing leading to labelling a patient as diabetic if his urine was ‘honeyed [1].

Diabetic Mellitus Definition

Diabetes mellitus is a group of metabolic diseases involving carbohydrate, lipid, and protein metabolism. It is characterized by persistent hyperglycemia, as a result of defects in insulin secretion, insulin action or a combination of both, defective secretion and incorrect action.There are two main types of diabetes mellitus: Type 1 (insulin-dependent), and type 2 (non-insulin-dependent). Type 1 diabetes results by the

autoimmune destruction of the β-cells of the pancreatic islets and type 2 diabetes is caused from impaired insulin secretion and resistance to the action of insulin.Current epidemiological data reveal that 9% of adults, 18 years of age and older, has diabetes mellitus while it was estimated that in 2012, 1.5 million people died due to the disease. According to the World Health Organization, diabetes will be the 7th leading cause of death in 2030[2]

This chronic metabolic disease appears to have an increasing trend in coming years, as lifestyle has changed a lot in modern world.Currently, DM is considered as a life-threatening disease and it has various complications such as retinopathy, nephropathy,neuropathy and infertility as well as cardiovascular diseases that should be addressed in DM treatment [3].

DM is categorized into two types including type I diabetes (T1D) and type II diabetes (TIID). There are significant differences between TID and TIID. In TID, β cells of pancreas are destructed and it is considered as an autoimmune disease, leading to insulin secretion interference. However, the insulin levels are high in TIID and cells are resistance to insulin. Another kind of DM is gestational diabetes (GM). The other rare kinds of DM include monogenic diabetes and cystic fibrosis-related diabetes (DFRD) Among various kinds of DM, TIID is the most common one and comprises up to 90% of all DM cases [3].

Type 2 Diabetes Mellitus (T2DM) TIID is one of the most common metabolic disorders worldwide and its development is primarily caused by a combination of two main factors: defective insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond to insulin. Insulin release and action have to precisely meet the metabolic demand; hence, the molecular mechanisms involved in the synthesis and release of insulin, as well as the insulin response in tissues must be tightly regulated. Therefore, defects in any of the mechanisms involved can lead to a metabolic imbalance that leads to the pathogenesis of T2DM [4].

Progression of the disease makes insulin secretion unable to maintain glucose homeostasis, producing hyperglycaemia. Patients with T2DM are mostly characterized by being obese or having a higher body fat percentage, distributed predominantly in the abdominal region. In this condition, adipose tissue promotes IR through various inflammatory mechanisms, including increased free fatty acid (FFA)release and adipokine deregulation main drivers of the T2DM epidemic are the global rise in obesity, sedentary lifestyles, high caloric diets and population aging, which have quadrupled the incidence and prevalence of T2DM [5].

Diagnosis of diabetic mellitus

For diagnosing prediabetes and diabetes, several blood tests can be done, namely: •Fasting plasma glucose (FPG): helps in measuring blood glucose after fasting for 8 hours.

•HbA1C test: helps in measuring blood sugar levels over the period of previous three months. [6][7].

Venous plasma glucose is the standard method for measuring and reporting. However, in recognition of the widespread use of capillary sampling, especially in low-resource settings, values for capillary plasma glucose are provided for post-load glucose values . In asymptomatic people, repeat the test to

confirm the diagnosis, preferably with the same test, as soon as practicable on a subsequent day. If plasma glucose ≥18 mmol/L (325 mg/dL), or symptoms are present, measure urine ketones to assess degree of metabolic disturbance. If plasma glucose measurement is not possible, urine glucose testing can be used to confirm suspicion of diabetes in people with symptoms. A negative urine test does not exclude diabetes, but it excludes severe hyperglycaemia [8].

Management of diabetes Type 2 diabetes

The American Diabetes Association (ADA) uses the term medical nutrition therapy (MNT) to describe the optimal co-ordination of dietary intake with diabetic therapy (both pharmacological and non-pharmacological) to achieve a favourable outcome. MNT can be used as a primary, secondary or tertiary prevention measure in T2DM. Primary prevention measures of MNT are by modifying diets in high-risk individuals (i.e., pre-diabetes, obese etc.) to delay or prevent the onset of T2DM. Secondary prevention measures aim to achieve tight glycaemic control by dietary modification and, thereby, reducing diabetic complications in patients with T2DM. Tertiary prevention measures are to manage diabetes-related complications such as cardiovascular or renal disease in those with T2DM [9].

The major conventional classes of drugs for the treatment of hyperglycemia includes sulfonylure (enhance release of insulin from pancreatic islets); biguanides (reduces hepatic glucose production); peroxisome proliferator-activated receptor-γ(PPARγ) agonists (boosts the action of insulin); α-glucosidase inhibitors (interferes with absorption of glucose in the gut)[10].

These classes of drug are either administered as monotherapy or given in combination with other hypoglycaemics. Severe hypoglycemia, weight gain, lower therapeutic efficacy owing to improper or ineffective dosage regimen, low potency and altered side effects due to drug metabolism and lack of target specificity, solubility and permeability problems are the major drawbacks associated with the use of the above mentioned conventional drugs [11].

Relationship between Bacterial Infections and Diabetes

Diabetic mellitus is a known risk factor for certain Infectious diseases because diabetic individuals are an immunocompromised due to their uncontrolled diabetes mellitus notably hyperglycemia [12].Due to which there is a higher risk of number of other medical complications including eye problems and blindness, cardiovascular disease, lower extremity amputations and renal disease in diabetic individuals as compared to that in non-diabetic individuals. Among the various causative factors, hyperglycemia is one of the main culprits to impair the over- all immunity of diabetic patient via involvement of various mechanistic pathways. Immunocompromised state is invariable in all diabetic patients. Not all diabetic patients are immune-compromised .Except those patients having nonnegative effects of hyperglycemic environment that favors Immune dysfunction such as damage to neutrophil function [13].

Increased incidence and severity of bacterial Infections in diabetes has been linked to an impaired Innate and adaptive immune responses within the hyperglycemic environment [14].

Diabetes increases susceptibility to various types of infections that cause considerable morbidity and mortality. [15] .The most common sites of Infection in diabetic patients are the skin, soft tissues, urinary tract, and respiratory tract [15] .

Type of infections:

Diabetic Foot:

Diabetic foot is known as the set of syndromes in which neuropathy, ischemia and tion cause tissue alterations or ulcers secondary to microtrauma. When talking about etic foot, we refer to a foot that has wounds or ulcers, typical of a person with diabetes. Arises from a dysfunction of the peripheral nerves in this type of patient [16].The prevalence of diabetic foot varies according to age, gender and place of origin. In the

diabetic population, the prevalence of foot ulcers is 4-10%. It is more common in older patients. Around 15% of diabetics will suffer from foot ulcers, and up to 85% of patients.With ulcers will end up facing amputation [16,17]. The risk of developing a diabetic foot ulcer (DFU) and amputation increases with age and the duration of diabetes [16,17].

Urinary tract Infection:

The most common infectious disease in diabetic patients is type 2 urinary tract infection (UTI) [18]. In all of the articles reviewed, the UTI rate in women was higher than in men, which appears to be related to bladder neurological dysfunction, physiological bladder changes due to aging or shortness of breath, and proximity to the anus among women [19]. In American study conducted on a health ser vice data base with more than 70,000 patients with type 2 diabetes, it has been found that 8.2% were diagnosed with urinary tract Infection during 1 year with incidence increasing with age [20]. In another database study, It was also found that urinary tract Infections were more common In diabetic patients as compared to that of non-diabetic patients among 89,790 matched pairs of patients with and without type 2 diabetes mellitus[20].

Skin infection:

Patients with diabetes are significantly more likely to develop skin and soft tissue infections (SSTI), Including cellulitis, osteomyelitis, and postoperative wound infections [21]. In a large retrospective, multiyear study of more than 2 million patients with SSTI, 10% occurred in diabetics [22]. The SSTI complication rate in ambulatory patients was more than 5 times higher In diabetics than nondiabetics [22]. Similarly, In patients hospitalized with SSTI, the rate of complications was almost 5% In diabetics versus 1% innondiabetics[22]. Patients with diabetes admitted to the hospital with SSSI were more likely to have complIcations, such as bacteremia, endocarditis, and sepsis[22].

Tuberculosis Infection:

Diabetes mellitus alters specific cytokines, whichh play a role In the protection against tuberculosis (TB) and is a risk factor for the development of active TB [23-24]. Diabetes causes increased susceptibility to tuberculosis through several mechanisms, including hyperglycemia and cellular insulinopenia, which have indirect effects on macrophage and lymphocyte function[25]. Tuberculosis (TB) is a contagious, infectious disease, due to Mycobacterium tuberculosis (MT), which usually lasts throughout the life course and determines the formation of tubercles in different parts of the body[26]. In Africa, the frequency of tuberculosis in diabetic patients remains high at 4-15% [27].

C-Reactive Protein (CRP)

CRP was first described as a serum protein capable of precipitating C-polysaccharide Streptococcus Pneumonia cell walls during the acute phase of infective conditions in the presence of calcium [28].

C-reactive protein belongs to a conserved protein family called pentraxins and has been identified in several organisms ranging from arthropods to humans[29] . CRP participates in acute phase response to inflammation, infection, or organ trauma in humans, increasing up to 1000-fold within 24 to 72 hours[30]. CRP is found in several cell types, including neurons, epithelial cells, monocytes, lymphocytes, and smooth muscle cells. However, the CRP gene is primarily induced in the hepatocytes due to elevated inflammatory cytokines, dominantly IL-6 [30]

The CRP half-life is approximately 19 hours, and its average levels are generally presented as mg/L or mg/dL[30] .Nonetheless, CRP levels differ among laboratories since there is no optimized standard. Levels below 0.3 mg/dL are considered

physiological, while levels above 10 mg/dL indicate bacterial and virus infections and severe tissue damage[31].

CRP has both proinflammatory and anti-inflammatory properties. It plays a role in the recognition and clearance of foreign pathogens and damaged cells by binding to phosphocholine, phospholipids, histone, chromatin, and fibronectin. It can activate the classic complement pathway and also activate phagocytic cells via Fc receptors to expedite the removal of cellular debris and damaged or apoptotic cells and foreign pathogens. This can become pathologic, however, when it is activated by autoantibodies displaying the phosphocholine arm in auto-immune processes, such as idiopathic thrombocytopenic purpura (ITP). It can also worsen tissue damage in certain cases by activation of the complement system and thus inflammatory cytokine [32][34].

C-Reactive Protein and Diabetes

Chronic low-grade inflammation with production of high levels of inflammatory proteins has been implicated in the development of T2DM [33].

C-reactive protein (CRP) is considered to be a prime inflammatory marker of T2DM, which is produced by liver cells, and its expression is regulated by interleukin 6 (IL-6) and TNF-α, which are produced by adipocytes , Chronic inflammation with elevated levels of CRP has been associated with obesity, hypertension, heavy drinking, smoking, and low physical activity, A vast number of cohort studies, having noted elevated levels of CRP in male and female participants, suggested that CRP is a risk factor for development of T2DM, The relationship between CRP and T2DM is independent of insulin resistance and body-mass index (BMI) [34] .

It well known that CRP is a common inflammatory biomarker that is elevated in the blood of subjects with severe inflammation and diseases including T2DM and Cardiovascular disease . A study on a Chinese population reported that the level of CRP

was higher in T2DM patients than in normal subjects [34] Some studies also have shown that higher levels of CRP are positively associated with increased risk of developing diabetes [34].

The mechanism of the association between CRP and T2DM is still not known in detail. However, there are some explanatory factors including oxidative stress, (which is believed to implicate low-grade inflammation) and genetic factors such as family history of T2DM [34]

A European study has reported that higher levels of CRP were more strongly and independently associated with increased risk of T2DM in women than in men and that this did not change after stratification by age, smoking or alcohol status, obesity or family history of diabetes[34].

Accumulating evidence corroborates the crucial role of inflammation in T2DM pathologies [34] Low-grade inflammation characterized by elevated inflammatory protein levels, including C-reactive protein (CRP), is linked with T2DM pathogenesis [35]

CRP, the typical inflammatory biomarker produced in the liver, is regulated by adipocyte-derived proinflammatory cytokines, including interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) [36]. The level of CRP is usually low in healthy individuals but can elevate 100- to 200-fold or higher in acute systemic inflammation and is chronically elevated in patients with T2DM. [30] In individuals with T2DM, CRP levels range between 4.49 and 16.48 mg/L [37] .

The production of CRP may be triggered by many metabolic and inflammatory factors associated with the development of T2DM, such as increased blood glucose, adipokines, and free fatty acid levels. In addition, an increased level of CRP represents a reliable

predictor of vascular complications and progression of cardiovascular disease in diabetic patients[30].

Furthermore, numerous human and animal studies demonstrated the associations of elevated serum CRP levels with obesity leading to T2DM. These findings add to the notion that the inflammatory state demonstrated by higher CRP levels is an essential factor in the pathogenesis of T2DM, Since increased body fat and obesity are among the main factors in the development of T2DM, which are also associated with increased risk for progression of obesity-related IR and inflammation [30].

Previous studies about diabetes and C Reactive Protein (CRP):

In study assesses the influence of demographic, lifestyle, and medication in the association between CRP and mortality in a national sample of adults with diabetes Cross-sectional study of data from 1999 to 2010 National Health and Nutrition Examination Survey (unweighted n = 3952; Weighted n = 19,064,710). Individuals were categorized as having diabetes if told by a provider they had diabetes, were taking insulin or other diabetes medications, or had a glycosylated hemoglobin A1c (HbA1c) ≥ 6.5%. CRP was classified into four categories: normal (≤0.1 mg/dL); moderate risk (0.11–0.3 mg/dL); high-risk (0.31–1.0 mg/dL); very high-risk (>1.0 mg/dL). Higher risk for mortality was associated with a very high-risk of CRP (HR = 1.88 (95% CI: 1.27–2.78), being a current (HR = 1.49 (95% CI: 1.10–2.01) or former (HR = 1.34 (95% CI: 1.03–1.73) smoker, and taking insulin (HR = 1.60 (95% CI: 1.25–2.05), taking anti-hypertensives (HR = 1.50 (95% CI: 1.22–1.85), and having co-morbidities such as cancer (HR = 1.32 (95% CI: 1.05–1.66) and hepatitis infection (HR = 1.76 (95% CI: 1.07–2.91), while taking Metformin (HR = 0.62 (95% CI: 0.50–0.76) had a lower risk of mortality. [38].

Plasma C reactive protein (CRP) is a marker of inflammation, and increased plasma CRP is reported in many diseases, including cardiovascular disease, diabetes, metabolic syndrome, arthritis and malignancies, this study aimed to evaluate the association between plasma CRP levels and cardiovascular disease, metabolic syndrome, malignancies and other comorbidities. They concluded that the mean age was 46.7±0.37 years and the median plasma CRP was 0.58 mg/L (IQR 0.36–1.09). The mean plasma CRP levels were higher in participants with cardiovascular diseases and cardiovascular risk factors, osteoarthritis, rheumatoid arthritis, pulmonary tuberculosis, and several cancers, including gastric, colon, breast and cervix, than in the general population. In the multivariable analysis, plasma CRP concentration was associated with increased prevalence of hypertriglyceridaemia (OR 1.157, 95% CI 1.040 to 1.287, p=0.007), diabetes (OR 1.204, 95% CI 1.058 to 1.371, p=0.005) and metabolic syndrome (OR 1.228, 95% CI 1.112 to 1.357, p<0.001) after adjustment for socioeconomic and lifestyle characteristics. There was no significant association between plasma CRP level and cancers [39].

The liver-derived C-reactive protein (CRP) is a sensitive and systemic biomarker of inflammation, and has been associated with increased risk of developing type 2 diabetes in populations other than Chinese. Therefore, prospectively examined the relation between plasma levels of CRP and risk of type 2 diabetes (T2D) among a Chinese population [40].

Materials and Methods

1. Collection of Samples : Fifty five samples collected from patients with Diabetic Mellitus (DM), those patients attended to Diabetic Mellitus Consulting Center in Marjan Teaching Hospital / Babylon Province for two months starting from November 2022,

they included male and female, ranged from (30-80) years old and diagnosis of all patients performed according specialized physician. Multiple clinical data of DM patients collected according to data sheet designed for this research, including (gender, age, DM initiation date, family historty of chronic diseases, level of education, occupation, active bacterial infections, DM treatment and some other demographic characteristics), control group including 15 apparently healthy subjects.

2. C-Reactive Protein (CRP) Measurement:

C-Reactive Protein (CRP) measurement performed either digitally by certain instrumentfor processing whole blood sample to yield blood profile including CRP, or traditionally that based on the principle of latex agglutination. The reaction occurs between the human C-reactive protein and the corresponding anti-human CRP antibodies. In the case of a positive reaction, within 2 minutes, visible agglutination of latex particles can be observed.

-Materials required

Materials required to perform CRP assay depend on the type of method used. The laboratory equipment and supplies are necessary to detect CRP levels using the agglutination test method:

- Serum sample
- Positive and negative control
- Glass slide with six reaction circle
- Mixing sticks
- Test tube
- Saline
- A uniform suspension of polystyrene latex particles coated with anti-CRP antibodies.

-Qualitative Method

- Take all reagents and serum samples to room temperature before the test starts and mix latex reagent gently before use. Do not dilute the controls and serum.
- Place one drop of serum, positive control, and negative control on a separate glass slide using a (disposable pipette) dropper.
- Add one drop of CRP latex reagent to the drop of test specimen (serum) on each slide.
- Using the mixing stick mix the serum and CRP latex reagent uniformly over the entire circle. Immediately start a stopwatch, and rock the slide gently back and forth for 2 minutes.
- Observe the clump (agglutination) macroscopically.

Results and Discussion

Table-1- Demographic Factors (Gender, Age, Length, Weight):

Patient	Male	Female	Age	Weight	Length
No.	34	21	(35-79) years old	(50-119) kg	(150-183) cm

Table-2- Demographic Factors (Occupation, Residence, Family History for Diabetic Mellitus):

Patient	Occupation		Residence		Family history for Diabetic Mellitus	
	Employee	Non Employee	Urban	Rural	Positive	Negative
No.	21 m 9 f	10 m 15 f	23 m 17 f	8 m 7 f	34	21

Table-3- Demographic Factors (Education, Cigarette Smoking):

Patient	Cigarette Smoking		Education		
	Smokers	not Smokers	Primary	Secondary	University
No.	11 m 2 f	23 m 19 f	15	27	13

Table-4-DM Chronic Diseases:

Patient	Patients with Hypertension	Patients without Hypertension	Patients with Heart Diseases	Patients without Heart Diseases
No.	23 m 21 f	7 m 4 f	13 m 12 f	19 m 11 f

Table-5- Presence of Active bacterial infection in DM patients:

Active bacterial infection			
Having bacterial infection		**Not having Bacterial Infection**	
Male	**Female**	**Male**	**Female**
21	9	14	11

Table-6- DM Treatment:

Patients take Treatment No.	Treatment Type
11	**Amaryl**
16	**Glucophage**
22	**Insuline mixtard**
6	**Different treatments**

Table -7- CRP Values:

Patients	Males with Bacterial infections	Female with Bacterial infections	Male without Bacterial infections	Females without Bacterial infections
No.	15	8	19	13
CRP Range	11.7 -22.9 (mg/l)	10.9 - 19.3 (mg/l)	10.8- 16.64 (mg/l)	10.5 - 14.56 (mg/l)

**** Note: all control group subjects have CRP values ≤ 10 mg/l.**

Discussion:

There is interest in using blood C-reactive protein (CRP) to predict adverse prognosis outcomes patients with type 2 diabetes. In cohort studies the analyses results of randomized controlled trials involving 22,322 type 2 diabetes patients were included. Meta-analysis indicated that type 2 diabetes patients with the highest CRP level had a greater risk of all-cause mortality (RR 2.03; 95% CI 1.49–2.75) and cardiovascular mortality (RR 1.76; 95% CI 1.46–2.13) [41].

The mean (SD) concentrations of hs-CRP were 2.79 (2.65) and 1.86 (2.03) mg/L, respectively, in cases and controls ($P < 0.001$). After multivariate adjustment for T2D risk factors such as lifestyle, body mass index, plasma triglycerides and HDL cholesterol, the hs-CRP was 1.74 [95% CI 1.12–2.70; P for trend = 0.016], when confined to the other 292 subjects with HbA1c <6.5% and their controls, the corresponding OR was 1.24 (95% CI 0.64–2.39; P for trend = 0.93) [40].

Although “normal” CRP levels vary from lab to lab, it is generally accepted that a value of 0.8-1.0 mg/dL (or 8-10 mg/L) or lower is normal. Most healthy adults have CRP levels lower than 0.3 mg/dL. A minor elevation in CRP level—generally 0.3 to 1.0 mg/dL—does not necessarily mean that the patient have an illness which require treatment. CRP levels may be higher in females, patients on hormone replacement therapy and those with high body mass index, in addition to variations in laboratory methods and reference ranges, all these factors could affect interpreting the CRP test results. A CRP level higher than 1.0 mg/dL usually suggests that there is inflammation in the body, but it does not identify the cause or the location of that inflammation. Very high levels of CRP can be associated with various types of infections, autoimmune diseases, some cancers and conditions affecting the lungs or pancreas [42, 43, 44, 45].

In study conducted for the first time, showing that delaying surgery in patients with elevated serum-CRP levels suffering from femoral neck fractures may lead to worse survival and increased complication rates. Furthermore, the overall postoperative complication rate (pneumonia and UTIs) was increased in the patients with elevated serum-CRP levels and delayed surgery. The mortality rate of the patients with elevated CRP and delayed surgery was significantly higher than that of the patients with normal serum-CRP levels (24% vs. 14%) [46].

Conclusion:

Diabetic Mellitus is an inflammatory condition associated with a high prevalence of several physiological diseases especially microbial infections such as bacterial or fungal infections which needed more researches and investigations especially for immunological fields, in addition, detection of CRP values (besides other important immunological biomarkers) continuously in DM patients may be valuable biomarker and indication for other problems including cancer, osteoporosis, cardiovascular diseases , detection of sepsis in early stages and others. Small increases in CRP predict the likelihood of developing cardiovascular events both in diabetic and non-diabetic populations. There is some evidence that CRP, besides its predictive role in determining cardiovascular risk, may represent an active participant in atherogenesis. Moreover, detection of high-sensitivity C-reactive protein (hs-CRP) test is requisite for DM patients, because hs-CRP test is more sensitive than the standard CRP test measuring slight increases in CRP levels even when within the normal range, because of this greater sensitivity, the hs-CRP test can help determine the risk of cardiovascular disease (CVD). Studies have shown that a single elevated hs-CRP level may be predictive of a myocardial infarction, stroke, peripheral vascular disease, and sudden cardiac death.

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