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Review Article

C-Reactive Protein, a Surrogate for Diabetes Nephropathy: A Systematic Review

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ABSTRACT

Over 415 million people have diabetes mellitus (DM) and among them, 40% develops diabetes nephropathy (DN). Because of DN, 5 to 15% end up developing end-stage renal failure (ESRF). Diagnosis of DN includes; urinary albumin excretion (UAE) persistently at 30 mg/day to 300 mg/day, and greater than 300 mg/day, in microalbuminuria and macroalbuminuria respectively. Another method is the glomerular filtration rate (GFR) or creatinine clearance rate < 60 ml/min, as calculated from a simplified MDRD formula.

DN follows a very complex pathogenic process. However, a large body of evidence demonstrates that, inflammation is key to events related to the development and progression of DN. Most epidemiologic reports based on observational studies investigating the hypotheses that inflammation is a risk factor in the development of DM and DN, have constantly agreed on a relationship found between CRP and nephropathy, by consistent findings that, the increasing CRP and pro-inflammatory markers independently correlates positively with DN. CRP's release is mediated by the pro-inflammatory cytokines. The pro-inflammatory cytokines known to be involved in DN includes: interleukin-6(IL6), interleukin-1 (IL1), and tumor necrosis factor alpha (TNF-α). A better understanding of a detailed mechanistic involvement of CRP-DM and CRP-DN related pathologic processes will be beneficial for future in both medical research and clinical settings, where CRP might serve to reveal new avenues for the prevention and or treatment of both DM and DN.

Conclusion: In DM, microalbuminuria is accompanied by elevated CRP levels, suggesting activation of inflammatory pathways in progression of renovasculopathies.

Keywords: Diabetes Nephropathy, C-reactive Proteins, Pro-inflammatory cytokines, Inflammation, Albuminuria.

INTRODUCTION

Diabetes nephropathy (DN) is a reversible multistage disorder, however if it is left neglected it may lead to kidney failure or End Stage Renal Disease. In diabetes mellitus (DM), microalbuminuria serves as a generalised early indicator for renal injury [1] and is also a marker of vascular endothelial damage [2-5] however on the other hand, inflammation is in addition novely known for its pivotal role in the enhancement of the pathogenesis of renal and cardiovascular diseases (CVD) in epidemiologic settings [6-9], such knowledge is untraditional in most clinical settings. As such one can want to extrapolate and would also be propelled to anticipate that, perhaps DM and Inflammation have some form of synergism with regard to them as risk factors amplifying thedevelopment of renal and CVDs. Although C-reactive protein (CRP), a marker for inflammation and a classical cardiovascular risk factor, is suggested on various accounts that, it is associated with the early processes leading to kidney damage, itself (CRP) and nephropathy (microalbuminuria) are both associated with increased risk for mortality [10]. The CRP and microalbuminuria associations can exist significantly, as either dependent or independent of the other traditionally known risk factors for kidney failure, like in poor glycaemic control in diabetes mellitus (DM), hypertension and others [11-13], however with regard to mortality risks, the associations of these clinical markers (CRP and microalbuminuria) are not only independent of conventional cardiovascular risk factors, but they are also independent of each other [10]. Nevertheless that CRP may be associated with nephropathy, it is the microalbuminuria status that is traditionally known to serve as a marker for early kidney damage [14], and in the same tone microalbuminuria is not restricted to only being considered a very well known risk factor for progressive kidney disease [15,16] for it is also a very well known considered

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risk factor for cardiovascular (CV) morbidity [17,18] and mortality [19].

Because DN is the most common cause of end stage kidney disease in the whole world [1], and the evidence clearly points that whether be it in diabetes or be it not in diabetes, CRP and nephropathy are positively related to each other and they (CRP and nephropathy) can also be strongly independently associated with CVD, irrespective of the known cardinal risk factors for CVD. Furthermore of note is that, in diabetes the decline in kidney function is highly variable [20] and is due to multi-factorial reasons. This systematic review focuses its attention on how the pro-inflammatory cytokines relates with DN, and how their intrinsic metabolic processes are associated with CRP, and finally its (systematic review) attention is projected on the subsequent associations found between CRP and DN. This systematic review aim was to analyse the associations of CRP with DN in populations with diabetes mellitus, grounded in the hypothesis that CRP is a surrogate marker for DN.

C-REACTIVE PROTEIN AND INFLAMMATION

Although CRP is dubbed as the most extensively studied inflammatory marker in both research andclinical settings, it is relatively recent that the epidemiologic studies concerned with DM to have now shifted their attentions towards investigating extensively, the C-reactive protein's relationship with low degree inflammatory activation, endothelium activation, and nephropathy. In many instances in research it has been demonstrated that, increasing CRP levels within the "normal" ranges is associated with increases in risks for CVD both in patients with history of CV events and in apparently healthy volunteers [21-23]. The latter vests the same power factor in subjects with DM, where this positive correlation between elevations in serum CRP concentrations and increased CVD risks exist in patients without any history of clinical macrovascular disease, and or microalbuminuria.

Although CRP, amember of the pentaxin family proteins [24], might be known as an acute-phase protein produced by the liver cells in response to various stimuli (Saraheimo, *et al.* 2003) to aid the clearance of necrotic and apoptotic cells [25], its production and supply may however also have an adipose tissue related background. This background is also in accordance to the extrapolations by Navarro and Mora [26], and Hotamisligil*et al* [27-43], that the increases in CRP levels is related to adipose-tissue-derived cytokines. This view that adipocytes is a production source for pro-inflammatory cytokines and the resultant mediator for CRP synthesis and release is further substantiated in DM subjects, by a much stronger correlation found between BMI or visceral obesity and CRP versus a less stronger correlation observed in non DM subjects [29].

A more physiologic picture that may further clarify the suggestion that serum CRP production is effectively drawn from the adipose tissue, is first and far most by an acknowledgement of the fact that interleukin-6 (IL6) pro-inflammatory cytokines and serum CRP arephysiologically integrated. Roughly about 15 to 35% of IL6 is derived from adipose tissue, mainly the omental adipose tissue [9,30], and several studies have demonstrated that IL6 is the main stimulus for the hepatic production of CRP (Saraheimo, *et al.* 2003). Some of the IL6 is produced from a variety of other cell types. Cell types such as activated leukocytes, myocytes and the endothelial cells [9,30-33]. The other pro-inflammatory cytokines that are involved in the mediation of CRP synthesis, include but are not necessarily limited to interleukin-1 (IL1), and tumor necrosis factor alpha (TNF-α) [21,34].

PRO-INFLAMMATORY CYTOKINE MEDIATED INFLAMMATION AND DIABETES NEPHROPATHY

The early detections in end-organ damage, is steadily becoming an essential tool that aids the facilitation or the guidance of treatment decision in diabetic individuals. In clinical facilities, the early expressions of kidney damage or DN, can be detected during a screening contact, and is indicated by proteinuria. Diabetes nephropathy is a devastating late complication DM, usually expresses itself as proteinuria when urinary albumin excretion (UAE) ranges is 30 to 300 mg/day (microalbuminuria) or when UAE is persistently greater than 300 mg/day (macroalbuminuria), and can further interchangeably express itself by decreases in the estimated glomerular filtration rate (eGFR) [35,36].

The hypothesis that chronic low grade inflammationleads to DM development because it elicits diseases instead of repairing, has been ongoing since the late 90's [29,37], and a great deal of data appreciates the fact that DM has an inflammatory component [38,39]. To a certain degree this hypothesis seems relevant also to microalbuminuria because microalbuminuria is considered by many authors, a marker of endothelial damage and is associated with higher prevalence of DM, hypertension, metabolic syndrome, renal dysfunction, and with an increased risk for CVD [40-42]. More so that in countless times a large number of studies have continually demonstrated that endothelial dysfunction is linked with inflammation [31,43-45].

The studies that invested its times on investigations around the notion that, inflammation is involved in the development of diabetes related microvascular complications had already begun to exist not so long ago in the early 90's with others under the leaderships of prominent authors like Hasegawa *et al.* [46] and others. But more recently, studies emanating from the foundation works laid by latter researchers have successfully demonstrated that, the inflammation and more specifically the pro-inflammatory cytokines plays significantly determinant roles in the development of microvascular complications in DM. In chronic hyperglycaemia, microvascular complications occur partly because these molecules (the pro-inflammatory cytokines) are dysregulated. For instance in hyperglycaemic status there is a profound accelerated production of endogenous TNF-α in the microvascular tissues, which subsequently results in enhancement of the microvascular permeability and or hypercoagulability. This illustration fits very well with the pathophysiologic mechanisms that are involved in DN, like the detections of proteinuria that might be as a result of increased glomerular permeability. Other inflammatory bio-makers that have been implicated and found to be reciprocal in DN pathogenesis include CRP, fibrinogen, IL1, and IL6 [47]. Another mechanism that yields DN can be drawn on the basis of the elevated levels in IL1 pro–inflammatory cytokines [48]. The IL1 is involved in the proliferation of mesangial cells and matrix synthesis, as well as in the development of intraglomerular microcirculatory abnormalities, primarily because it increases the vascular endothelial permeability. With regarded to the mesangium, the other pro-inflammatory cytokine that appears to show its foot print is the Interleukin-6 (IL-6), for in accordance to Shikano and others, IL6 mRNA expressions have been found in

the mesangium of renal specimens from diabetic subject.

In the face that a large number of studies have convincingly confirmed that different types of interrelated pro-inflammatory cytokines can be independently associated with CRP, and or DN. And whilst this current review (study) proceeds to inspect very closely the links between CRP and DN, it will be important to make a background note that, the increasing concentrations of some of thepro-inflammatory cytokines and CRP in DM are inversely associated with glucose disposal rate [15,49], for this then indicates that hyperglycaemia might have a dual progression promoting factor involved in the genesis of inflammation and DN , as it has been proven in works of some of the fellow researchers like Pickup *et al* and more recently in 2008 by Choudhary and Ahlawat [37]. However some of the investigators have found the role of hyperglycaemia, particularly towards the progression of DN to be less clear, in part due to lack of statistical power [1,50,51], but this was contrary to the findings by Rossing, *et al* andChoudhary and Ahlawat [37,52], for they found that glycated haemoglobin was significantly associated with DN. It will furthermore, be important to also make an additional background note that a several line of studies have demonstrated the existence of microalbuminuria in DM in terms of its relationship toage [34,53,54], and most studies have observed that microalbuminuria is more pronounced and is more significant in older patients that have been affected by DM longer, than inyounger patients who have been affected by DM less longer. Such a similarity of rather a rare chance for a development of nephropathy in diabetic patients of less than 10-year duration has also been echoed in a study by Martha and Femando [55,56]. This might as well be one of the apparent explanations to why the mean CRP level tends to be more drawn to a significantly higher mark in older diabetic subjects in comparison to the younger diabetic counterparts with a significantly lower mark [2].

A several number of studies have demonstrated that, serum CRP concentrations are positively associated with proteinuria in diabetic subjects. In both types (type 1 and type 2 DM), the serum CRP levels are higher in microalbuminuria subjects when compared with those with normoalbuminuria [13,57].

However some authors have been able to confirm the significant association between baseline serum CRP levels and the development of DN, when it comes to the associations between serum CRP levels and the subsequent or prospective risk for DN progression they were not able to observe any significant relations [10,52,57]. Like the findings in Schalwijk, *et al.* [31] report, which have indicated that they did not observe any significant differences in serum CRP levels of diabetic subjects with microalbuminuria and macroalbuminuria? This latter finding talks to the fact that although that CRP can be used as surrogate to predict the occurrence of DN in diabetes, it appears that from a point where DN has occurred or is confirmed, further facilitation of DN progression via additional mechanistic processes beyond CRP begins. Which means, this process (DN progression) from that moment and onwards, might be potentially progressing independently of the effects of CRP or it might be actually continuing to progress synergistically under the effects of CRP (Table 1).

Table1: Studies that have found the associations of serum CRP levels and DN.

Studies/Authors	Nature of the study
Hayashino et al, 2014	Longitudinal
Sabanayagam et al, 2010	Cross-sectional
Mojahedi et al, 2009	Cross-sectional
Choudhary and Ahlawat, 2008	Longitudinal
Navarro et al, 2005	Review
L IAO et al, 2004	Longitudinal
Saraheimo et al, 2003	Cross-sectional
Coen et al, 2002	Longitudinal
Schalkwijk et al,1999	Cross-sectional

C-REACTIVE PROTEIN AND ANTIOXIDANTS

Diabetic subjects are known to have increased levels of oxidative stress and inflammation, and the literature has for a relatively long time always suggested that inflammation and oxidative stress are involved in the pathogenesis of vascular diseases [17,58]. The implication that inflammation and oxidative stress is base for the development of vascular pathogenesis is that, the oxidative damage on the arterial wall by free radicals results in the stimulation of endothelial cells by the CRP and subsequent the promotion in the expression of cellular adhesion molecules (CAM), which in turn will facilitate the adhesion of monocytes and T cells to the arterial wall in the first steps of the atherogenic process [59]. The atherogenic process will subsequently result in endothelial dysfunction, which is a major characteristic of vascular diseases [60]. The manner in which oxidative stress facilitates endothelial dysfunction is that it alters the expression of the nitric oxide synthase (NOS) and the nitric oxide (NO) metabolism [61]. The alterations of the endothelial nitric oxide synthase results in failure to produce enough NO which in turn is supposed to aid in vasodilation and to a certain extent also further aid in the anticoagulant and anti-inflammatory properties of the endothelium.

Oxidative stress is observed when the body's oxygen levels far exceed the cell's anti-oxidant activity. A variety of antioxidants are either produced by the body or provided by dietary, and they act as the body's defence compounds or reactive oxygen sp scavengers for they neutralize the free radicals by providing them with electrons. They are able to give away electrons without them necessarily becoming reactive at the end. But unfortunately this process is destabilized in chronic hyperglycaemia.

The antioxidants are inversely related to the synthesis of inflammatory markers including serum CRP levels [49]. The antioxidants effects have been illustrated very well in previous studies, with some of those studies portraying how the antioxidants mays actually contribute to the overall improvement of the total antioxidant capacity (TAC) of diets. The synergistic effect of antioxidants and TAC of a diet was demonstrated in a study by Brighenti and others [49] with findings indicating an inverse association with markers of systemic inflammation, including hs-CRP and others. A similar finding of decreases in serum CRP levels due to antioxidants and TAC of a diet was also observed by Hozaw and colleagues [62] from a data that was analysed both cross-sectionally and longitudinally in the same study subjects. Valtuena *et al.* [63] took it a step further in an analysis done on healthy subjects, where they analysed the effects that a higher dietary TAC diet might have on oxidative stress, low-grade inflammation, or liver dysfunction, in comparison with the effects that a lower dietary TAC diet has. The results showed that plasma hs-CRP levels, liver enzymes concentrations decreased significantly in a group subjected to a higher dietary TAC diet intervention compared with the ones subjected to a lower dietary TAC diet intervention. These findings are very important because the rise in hs-CRP levels and the rise in liver enzymes

concentrations are associated risk factors for T2DM and CVD.The liver is not only included because it plays an essential role in the glucose homeostasis, but it is intentionally included because it is also involved in the oxidative processes and the detoxification of major metabolites produced as end-products of excessive oxidation or oxidative stress [64]. In simple terms in the event that the liver functions deteriorates, and its ability to store glucose is affected, then this will potentially exacerbates hyperglycaemia and oxidative stress, which in turn can unfold a vicious cycle that may see an establishment of vascular complications. A vicious cycle in a sense that; oxidative stress activates other pathogenic pathways and those pathways will make injury via oxidative stress, and the oxidative stress will directly lead to injury [56]. For example in a study by Esposito *et al.* [65], they found that hyperglycaemia acutely increases circulating cytokine concentrations by an oxidative mechanism. Esposito *et al.* [65] report showed that if plasma glucose levels were acutely raised in people without diabetes while endogenous insulin secretion was blocked, they would experience a significant rise in pro-inflammatory cytokines. Furthermore in their findings they demonstrated that if you have two groups, one group of subjects with impaired glucose tolerance (IGT) and the other one of subjects with normal glucose tolerance (NGT) and subject both these groups to intravenous glucose pulses, you would find that the pro-inflammatory cytokine peaks would be higher in the IGT subjects than those of the NGT subjects. Lastly, they further illustrated on another occasion that if you again subjected these groups to the same glucose pulses during an infusion of glutathione; there would not be any significant change in the pro-inflammatory cytokine levels.

Very interesting is the knowledge that, the effects of most of the antioxidants and higher TAC diet can still be effective even if the effects of some of the well known factors of inflammation, such as alcohol, fibre, vitamin C, α-tocopherol, b-carotene, BMI, waist circumference, high density lipoprotein (HDL)-cholesterol, hypertension, insulin sensitivity and plasma β-carotene, have been statistically omitted or adjusted. Fruits and vegetables are the main sources of dietary antioxidant vitamins and as such the dietary TAC is directly influenced by them. The dietary antioxidant are particularly important in inflammation, because they also constitute a great deal in variety of the bioactive compounds, like thepolyphenols, which has antioxidative properties that enables it to act at different levels of the inflammatory cascade [51]. However the anti-inflammatory effects carried in by the antioxidants and dietary TAC are well appreciated in vitro [66,67] and in some of the epidemiological studies, their effects in vivo studies shows inconsistent results, especially when a dietary rather than a pharmacological amounts are used [45,68-70].

DIABETES MELLITUS, DIABETES NEPHROPATHY, AND ANTIOXIDANTS

Although experimental studies have established the role oxidative stress as one of the key factors involved in the pathogenesis of diabetes nephropathy and its complications [64], there are other several mechanisms that are involved in the pathogenesis of diabetes nephropathy and its complications, and the fact is that all of these mechanisms originate from hyperglycaemia [71,72]. Some of the researchers like Ceriellohave failed to prove the beneficial effects of some of the classical antioxidants like vitamin E, when used in diabetic patients. In fact it was found that high dosages of vitamin E could not prevent albuminuria whilst the lower dosages were found to exacerbate the renal injury [57,73], however some researchers have found that oral vitamin E treatment is effective in that it can normalize elevated baseline creatinine clearance in T1DM patients. While it was found by Gaede *et al.* [74] that supplementation of vitamin E (680 mg/day) and vitamin C (1250 mg/day) in T2DM people was associated with significant improvements in renal function.

CONCLUSION

CRP is conclusively positively associated with DN in both, cross-sectional and or prospective manners. Therefore this finding should see, the increasing serum CRP levels being used as a generalized surrogate marker for DN in both medical research and clinical practice in the future. Leaving CRP levels as a modifiable risk factor that can serve for new avenues in the treatment and prevention of DN.

Plus, CRP intrinsically interrelates positively with a variety of pro-inflammatory cytokines, and high serum CRP levels acts as a representation of this phenomenon, as a result in this review I have therefore made use of a panel of pro-inflammatory cytokines to establish their relationship with nephropathy, and evidently, they all were positively associated with DN.Concluding that in diabetic patients, low grade inflammation is present already at the very early stages of DN.

RECOMMENDATIONS

More studies that seek to describe the associations between serum CRP levels and DN should be undertaken, so that we can arrive to a scientific conclusion to agreeing that increasing serum CRP levels can be used as a generalized surrogate marker for DN or the development of DN in clinical practice in the future.With such a particular understanding of the clinical characteristics and risk factors associated with the development of DN or the progression of DN, perhaps a platform for the development of newer effective therapeutic strategies to prevent the onset and or the progression of DN may be established, using CRP itself as a therapeutic target.

Such platform should be in concert with further research studies on the significance of the roles that the antioxidants might be playing towards the sequestration and the modulation of the pro-inflammatory bio-molecules and CRP. Especially with a background that several epidemiologic data has already showed a beneficial direction in participation that the antioxidants has with markers of inflammation, oxidative stress, and endothelial dysfunction. Those studies might potentially further add to an emphasis of the relevance of strategically placing antioxidants as optional measure available to the prevention or the treatment of diabetes microvascular complications like DN. The investigations are of vital importance, because it is mainly these pro-inflammatory cytokines themselves that act as stimuli for the CRP's hepatic production and the resultant inflammation in the first place.

RESEARCH METHODOLOGY

I conducted this systematic review in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Protocol.

SEARCH STRATEGY AND SELECTION CRITERIA

I searched the PubMed database and Google Scholar database up to

2017, searching for observational studies looking at the association between inflammation and diabetes nephropathy.

This study analyses was restricted to human studies published in English language. The observational studies were restricted to peer-reviewed cohort reports, case-controlled, or cross-sectional studies that presents a quantitative relationship between CRP and DN. This study has also included studies that compared the association of CRP and DN as is observed in a diabetic populations (classified as: normoalbuminuria, microalbuminuria, or macroalbuminuria), to a general population as long as they had performed stratification or standardization by age groups. The study has included both the normotensive subjects and the hypertensive subjects with a systolic BP>140 mmHg or a diastolic BP> 90 mmHg for the latter subjects. This inclusion criterion serves to control the effect that BP has on diabetes in terms of the risks for the development of CVD and nephropathy, for a good BP control is known to be important in preventing adverse cardiovascular and renal outcomes in diabetic subjects [75]. Furthermore for subjects (diabetics and or controls) on high blood pressure (BP) medication, they were included only if their BP measurements were less than 160/100 mmHg. This criterion is informed by the fact that arterial BP >160/100 mmHg is regarded as a severely uncontrolled arterial hypertensive status and is a confounding factor for proteinuria [37]. Although history of cigarette smoking is also a known confounding factor for proteinuria [37] this study has included subjects with cigarette smoking history. However there is a study by Sah *et al.* [25] with rather somewhat cliché findings, for they could not find any significant correlations between serum CRP levels and smoking. Meaning that, an increase in serum CRP levels might not be necessarily dependent on diabetes nephropathy's environmental risk factors, such as smoking. However, Chen-Chung *et al.* [76] have demonstrated that there are significant associations between serum CRP levels and smoking. Therefore this review has indicated where necessary the effects that smoking had on CRP, in order not to take for granted the values that studies like Rossing*et al* and others, has in clinical research, where they have shown that smoking status is predictive of the declining rates in kidney function.

DATA EXTRACTION

The investigator (PP Maduna) has independently read the papers and has extrapolated information pertaining the studies' findings, he beard his focus on the given definitions for DN, study populations, pro-inflammatory biomolecules, and on associations found between serum CRP levels and DN in accordance to their statistical significance, to develop this systematic review.

ETHICAL CONSIDERATION

This study is a systematic review, and subsequently it incorporated observational studies that have already abode by the institutional guidelines and terms of the Helsinki Declaration of 1975 regulations regarding investigations among human participants, and therefore no further approval is required from Ethics Review Board of the South Wales University.

Participants were not benefited directly in this systematic review, but if this study confirms that CRP is a surrogate marker for DN, then CRP could be used in clinical practice to ascribe a description for risk of future DN development. The finding may also assist researchers to update, develop, and adopt evidence based guidelines for the prevention and treatment of DN.

The student (researcher) involved in the study has subsequently with his experience gained further knowledge and skills in this scope of diabetes care (clinical medicine) and this field of research.

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