IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 1 Ver. 3 (January. 2019), PP 42-48
www.iosrjournals.org

Feasibility of Platelet Indices as Possible Biomarkers in Evaluation of Initial Vascular Risks in Non-Diabetic Subjects.

Rajiv Kumar Ranjan[1*], Sabiha Ashraf[1], Sompal Singh[1], Harender Beer Singh[1], Madhur Kudesia [1], Rakesh Sharma[1,2]

[1]*Department of Biochemistry, Hindu Rao Hospital, Delhi-7*
[2]*Innovations and Solutions Incorporated USA, 3150, Philips Highway, Jacksonville, Florida 32207 Phone: 09548336632*
Corresponding Author: Rajiv Kumar Ranjan

Abstract: *A possible role of platelet indices in non-diabetic subjects was explored for its possible association with hematopoietic and renal biochemical indices. Hypothesis was that non-diabetic disease burden is closely associated with change in serum levels of lipoproteins, urea, uric acid, creatinine, microalbumin and hematological parameters as consequence of platelet dysfunction manifested as dyslipidemia, nephrosis and thrombosis. A total of 97 non-diabetic patients out of 225 were analyzed for correlation and contribution of serum sugar, lipoproteins, urea, uric acid, creatinine, microalbumin and hematological parameters with platelet dysfunction as 'pleiotropic risk index'. Results showed that 'pleiotropic risk index' may reflect the initial trigger of dyslipidemia, followed by progressive renal complications with growing risk of thrombosis in non-diabetic subjects. Males in their fifties age were at high risk of pleiotropic effects. Change in serum levels of sugar, lipoproteins, urea, uric acid, creatinine and microalbumin contribute as pleiotropic factors with increased risks in the order of lipids < platelet indices < urea < creatinine < microalbumin < hematological parameters < uric acid. Deranged platelet indices were closely associated with initial vascular and renal complication in non-diabetic subjects. In conclusion, non-diabetic pleiotropic effects associated with platelet indices, biochemical and hematopoietic biomarkers served as better risk indicators of progressive vascular complications in non-diabetic patients having chronic kidney disease.*

Date of Submission: 20-12-2018 Date of acceptance: 06-01-2019

I. Introduction

Despite of the estimated prevalence of insulin independent type 2 diabetes at risk of vascular and renal complications closer to 50 million people in year 2000 with chances of high rise closer to 100 million in 2025, last decade explored possible role of previously unreported pleiotropic effects to increase the burden and risk of glucose independent dyslipidemia, nephrosis and thrombosis responsible to induce platelet dysfunction among non-diabetic subjects with prothrombotic tendency. Current evidences show that obesity, glomerular hyperfiltration, albuminuria, and dyslipidaemia might also adversely affect the kidney in non-diabetic subjects at risk of vascular and thrombotic complications. Control of these risk factors could have additional benefits on renal and cardiovascular protection outcome in patients at risk of chronic kidney disease. However, despite multifactorial treatment approaches, residual risk for the development and progression of diabetic kidney disease in patients with type 2 diabetes remains, and widely unnoticed in non-diabetic subjects. Novel strategies or therapies to treat the renal disease with or without diabetes are urgently needed (1). We analyzed these factors further as part of present extended ongoing study (1).

Platelet physicochemical changes observed as elevated MPV, increased PDW, large P-LCR, might trigger or contribute the risk of dyslipidemia, atherosclerosis, nephrosis, thrombosis in non-diabetic subjects (2-5). Still, association of pleiotropic effects such as environment, behavior, life style (habitual discipline of protection measures to keep diabetes, heart and renal disease in control), demographic and socioeconomic factors remains as a dilemma if platelet sub-physiological changes in non-hyperglycemic condition may indicate the risks of cardiovascular and renal disease.

Platelets show increased MPV initially leading to osmotic swelling as a result of raised blood hematopoietic and lipid metabolites precipitated with metabolic syndrome, stroke and diabetes (6). From biochemical standpoint, it is well established that increased insulin receptor number and poor affinity of insulin receptor on platelets might cause the reduced insulin sensitivity and increased platelet volume or platelet hyperactivity in non-diabetic subjects(7). However, elevated platelet size of hyperactive platelets during long time exposure to pleiotropic factors might serve as precursor in micro-vascular complications of endothelium dysfunction and atherosclerosis in non-diabetic subjects (8).

In non-diabetic subjects, the hyperlipidemia, thrombosis, renal derived changes in platelet membrane dynamics might also trigger the "vicious circle" to cause alterations in membrane fluidity, platelet activation, platelet release and platelet volume distribution to elevate platelet activity(9-11). Authors believe that dyslipidemia, renal dysfunction and platelet protein changes may modulate the platelet membrane dynamics to cause altered platelet indices with a consequence of thrombopoisis in non-diabetic subjects at high risk of lipid disorders and endothelium injury (1).

II. Materials and Methods

A total 97 non-diabetic control subjects (Group I) were analyzed for various hematological parameters like Hb, HCT, RBC COUNT, MCV, MCH, MCHC, RDW-SD, TLC,PC, MPV, PDW and P-LCR. RBC parameters were evaluated by fully automated auto analyzer.

Disease burden including dyslipidemia, renal dysfunction and thrombosis were evaluated in non-diabetic subjects (Group II) by % fold changes (significant different P values) in platelet parameters and associated biochemical, hematopoietic parameters predicting the non-diabetic complications of dyslipidemia, renal dysfunction and thrombosis. For it, comparative analysis was done by Mann-Whitney test for biochemical parameters including serum cholesterol, triglycerides, HDL, LDL, serum creatinine, microalbumin and urea levels in non-diabetic group subjects at risk and pleiotropic effects. P values were calculated. Comparative analysis was done by Mann-Whitney test for various hematological parameters like Hb, HCT, RBC COUNT, MCV, MCH, MCHC, RDW-SD, TLC,PC, MPV, PDW and P-LCR. RBC parameters of non-diabetic subjects with groups I, II, and III. P values were calculated. Multivariate analysis was done for evaluation of contributory factor(s) to demonstrate association of platelet indices (PC, MPV, PDW and P-LCR) with, biochemical or hematological factor.

III. Results and Discussion

Non-diabetic (control) Group I subjects were at no risk (n=22), or with one or more risk factors for dyslipidemia (n=30), renal dysfunction (n=25) and thrombosis (n=20). In these subjects, 41 cases had altered body mass index, 35 cases of smokers, 32 cases with hypertension at time of study, 52 cases with dyslipidemia and one case of chronic kidney disease.

In non-diabetic group without risk factors and non-diabetic groups (with risk factors of dyslipidemia, renal disease and thrombosis), mean age was 41.55 ± 12.44 years and 44.19 ± 11.19 years. In non-diabetic (n=22); and risk groups (n=75), different platelet indices are shown in Figure 1.

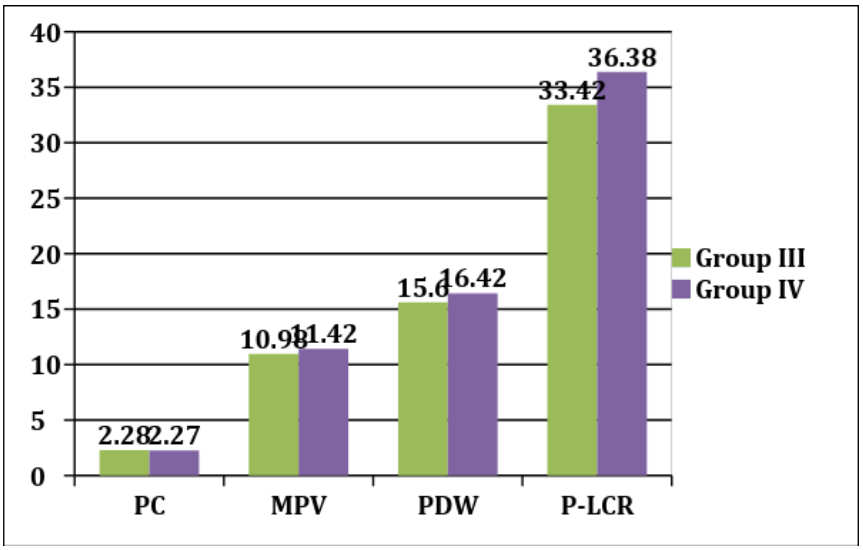

Figure 1: Non-diabetic risk burden by platelet parameters between various groups (Y-axis represents values of platelet parameters in conventional units): mean platelet count (PC) 2.28 ± 0.88 lac/cumm (range 1.50 to 4.97 lac/cumm in group I) and 2.27 ± 0.81 lac/cumm (range 1.00 to 5.21 lac/cumm in group II) with no significant statistical difference in PC value in groups I and II(P=0.823); mean platelet volume (MPV) 10.98 ± 1.10 fL (range 8.2 to 13.7 fl in group I) and 11.42 ± 1.42 fL (range 8.5 to 14.8 fl in group II) but strong statistical difference in MPV value in group I and group II(P=0.233); platelet distribution width (PDW) (15.60 ± 3.81 fL(range 10 to 23.2 fl in group I), and 16.42 ± 4.15 fL (range 10.6 to 25.9 fl in group II) but strong statistical difference in groups I and II(P=0.502); platelet large cell ratio (P-LCR) 33.42 +11.09 % (range 13.7 to 54.9 % in

group I) and 36.38 +11.34 (range 15.2 to 61.1 % in group II) with significant difference in PDW value in groups I and II(P=0.283).

Nondiabetic subjects without risk in group I and non-diabetic subjects having pleiotropic risks including dyslipidemia, chronic renal and thrombosis in group II showed a clear comparison for significant difference in figure 2 through figure 5 for serum cholesterol, triglycerides, HDL, LDL (dyslipidemia risk); in figures 6, 7, 8 for serum urea, creatinine, microalbumin (renal dysfunction risk); in figure 9 for hematopoietic parameters (thrombosis risk). Non-diabetic subjects clearly indicated the possible effect (level of significant differences) of glucose independent metabolic disorders by biomarkers including atherogenic lipids, renal excretory urea, creatinine and microalbumin analytes and thrombogenic proteins.

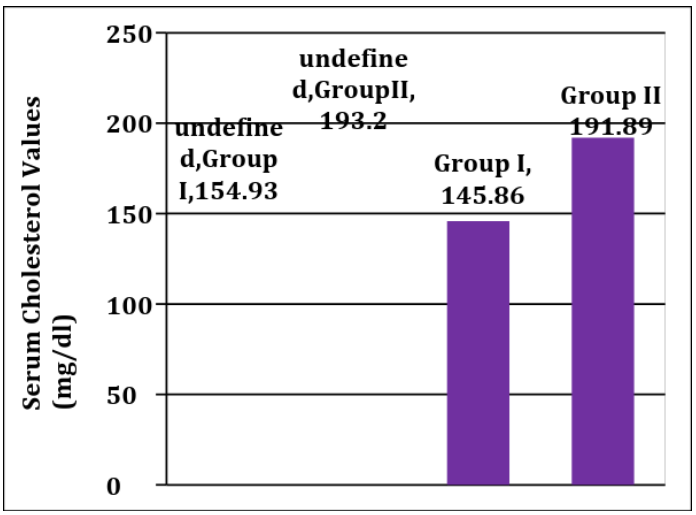

Figure 2: Non-diabetic pleiotropic risk burden by serum cholesterol values between various groups is shown as no significant statistical difference in groups I and II (P=0.014).

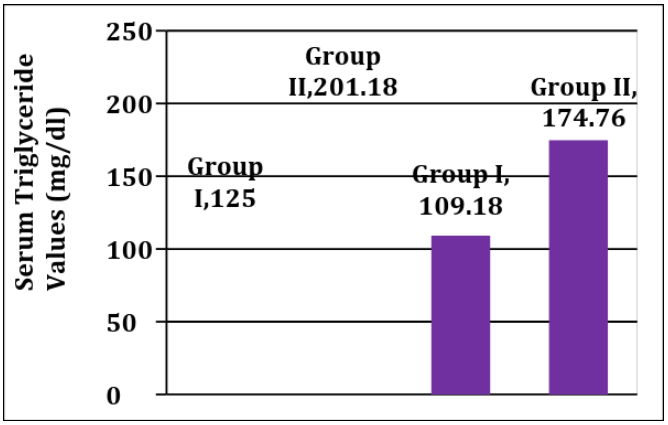

Figure 3:Non-diabetic pleiotropic risk burden by serum triglyceride values between various groups is shown as no significant statistical difference in groups I and II (P=0.006).

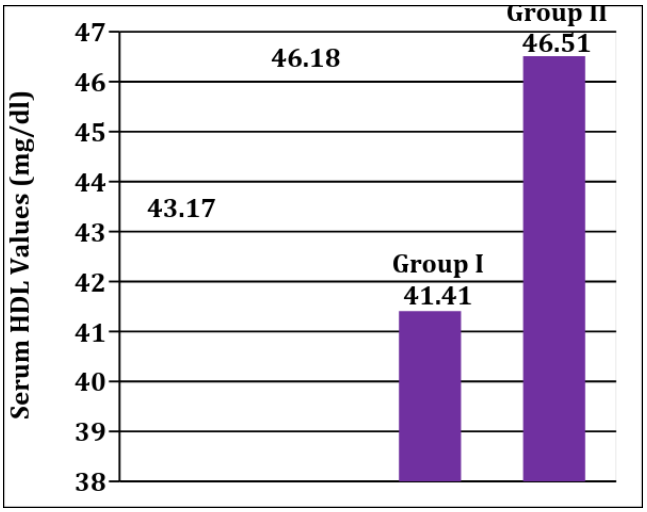

Figure 4: Non-diabetic pleiotropic risk burden by serum HDL values between various groups is shown as statistical difference in significant difference in groups I and II (P=0.022).

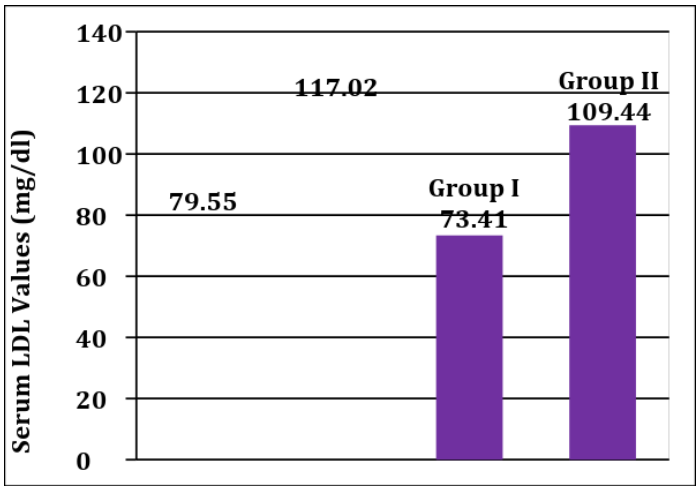

Figure 5: Non-diabetic pleiotropic risk burden by serum LDL values between various groups is shown as significant statistical difference in groups I and II (P=0.000).

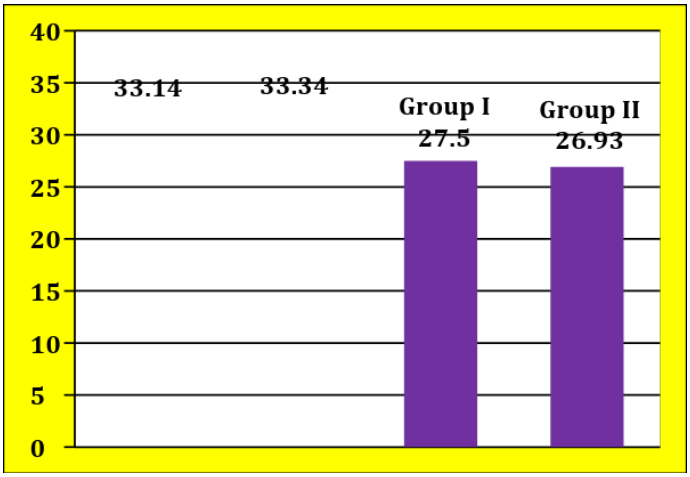

Figure 6: Non-diabetic pleiotropic risk burden by serum urea values between various groups is shown as significant statistical difference in groups I and II (P=0.000).

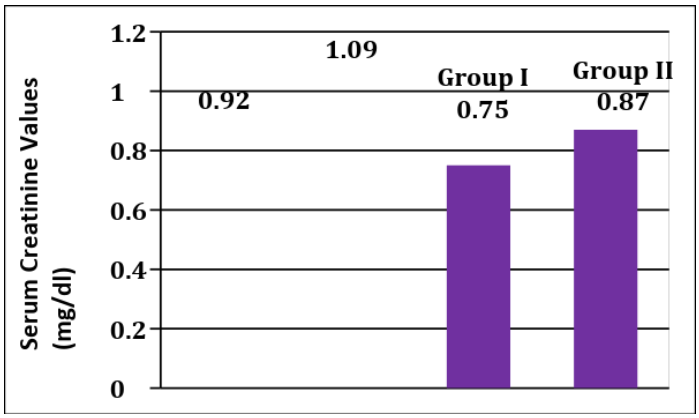

Figure 7: Non-diabetic pleiotropic risk burden by serum creatinine values between various groups is shown as significant difference in groups I and II (P=0.002).

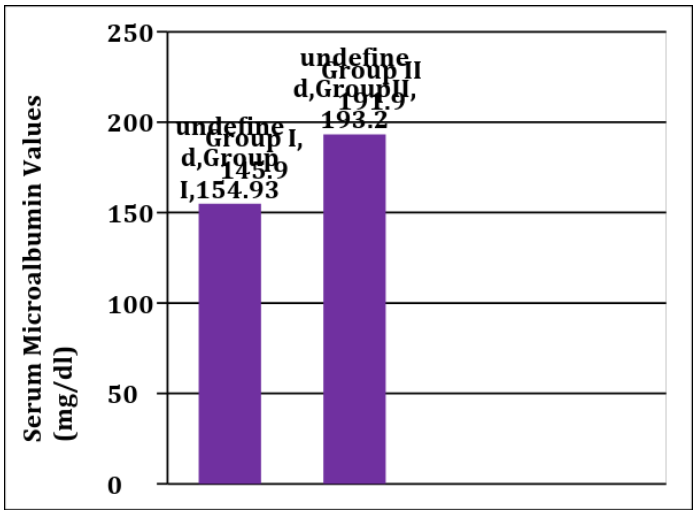

Figure 8: Non-diabetic pleiotropic risk burden by serum microalbumin values between various groups is shown as significant difference in groups I and II (P = 0,0001).

HEMATOLOGICAL PARAMETERS IN NON-DIABETIC SUBJECTS AT PLEIOTROPIC RISK

Hematological parameters Hb, HCT, RBC COUNT, MCV, MCH, MCHC, RDW-SD, TLC,PC and RBC parameters were evaluated in non-diabetic without risks (group I) vs with risks of dyslipidemia, renal dysfunction and thrombosis as shown in Figure 9.

TOTAL LEUCOCYTE COUNT (TLC)

Mean ± SD were observed in group I(n=22); and group II(n=75) of TLC: 1634.08 ± 145.45(range 4000-11000/cumm in group I), 7324.3±1989.42 (range 4100-15800/cumm in group II) with no significant difference in groups I and II (p=0.111).

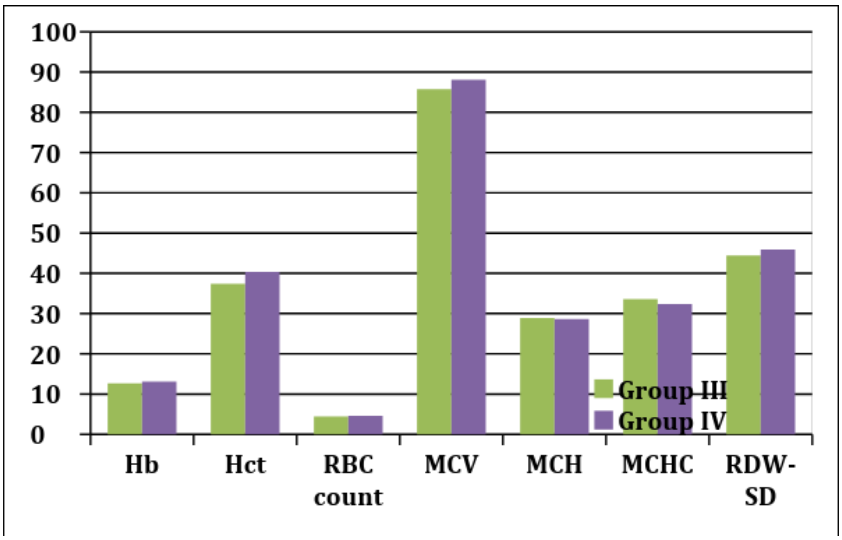

Figure 9: .Non-diabetic pleiotropic risk burden by RBC parameters between various groups (Y-axis represents values of red cell parameters in conventional units) is shown different biochemical parameters. Hb shows no significant difference in groups I and II. Hematocrit value show significant difference in groups I and II (p=0.007). RBC shows I and II. MCV reflects anisocytosis with no significant difference in groups I and II. MCH shows significant difference in groups I and II (p=0.001). RDW-SD shows no significant difference in groups I and II.

What are new lessons on Non-diabetic subjects at risk of Dyslipidemia, Renal dysfunction and Thrombosis?

- The pathophysiological changes of nondiabetic kidney disease involves complex interactions between metabolic and haemodynamic factors on a background of genetic predisposition. Oxidative stress and inflammation play major role (1).
- Chronic cardiometabolic abnormalities (including obesity, systemic hypertension, glomerular hyperfiltration, albuminuria, and dyslipidaemia) also contribute early on in the nondiabetic cardiac disease course.
- Multifactorial therapy may improve renal outcome in nondiabetic patients such as lifestyle interventions (eg, diet and exercise to achieve weight loss, right attitude and behavior, smoking cessation) and pharmacological management of glucose, blood pressure, antithrombic therapy and lipids.
- Renin-angiotensin-aldosterone system (RAAS) inhibitors have shown renoprotective effects alongwith decreasing blood pressure. RAAS inhibition has shown to attenuate the progression of diabetic kidney disease in trials, in which renal risk is high and/or the associated treatable cancers. However, residual risk of chronic kidney disease remains in nondiabetic patients such as microalbuminuria. It certainly alerts for novel strategies or new therapeutic drugs to reduce this residual renal risk in patients.
- UKPDS, VADT trials suggest the value of intensive glycaemic HbA1c control, BMI on renal outcome in patients with type 2 diabetes as recovery of reduced microalbuminuria, macroalbuminuria and doubled serum creatinine with reduction of microvascular disease (renal failure, retinal photocoagulation, or vitreous haemorrhage) to justify "legacy effect". Similar approach is needed for nondiabetic subjects (1).
- ADVANCE, ACCORD trials define a renoprotective effect of glycaemic control on diabetic kidney disease based on albuminuria reduction achieved with metformin, sulfonylureas, and insulin with possible for microvasculature cardio-protection (1).
- New proposal from authors on renoprotection beyond glycemic control in type 2 diabetes is possible by correction of pleiotropic effects such as obesity (hyperlipidemia) to reduce weight, hormonal, inflammatory factors, BMI, microalbuminuria, diet modification with exercise (life style interventions similar with AHEAD trial) to save kidney in nondiabetic subjects (1).
- Safe use of antihypertensive strategy as suggested by KDIGO/JNC8 (correct BP measurement and safe use of CCB, ACEI or ARB in diabetic CKD treatment) along with stepwise LOW ALCOHOL INTAKE-NO SALT-HEALTHY WEIGHT lifestyle modifications and drug therapy (similar with BENEDICT, ROADMAP trials) (1)
- Safe management of glomerular hyperfiltration and elevated albuminuria (similar with RENNAL and ACE-inhibitor trials) by corticosteroid treatment, protein restrictive diet, RAAS blockade limited benefits,

thiazolidinedione rosiglitazone, GLT-1 peptide, DPP-4 inhibitors (saxagliptin and linagliptin), SGLT-2 inhibitors (1).

- Careful treatment and management dyslipidaemia (hypertriglyceridaemia, decreased HDL cholesterol concentrations, high LDL cholesterol concentrations, obesity and insulin resistance) in patients with type 2 diabetes with or without chronic kidney disease, for reduction of microalbuminuria and cardiovascular risk and mortality.by statins (similar with PLANET I, FIELD trial guidelines) (1).
- Safe supervised use of thiazolidinedione, metformin+sulfonylurea, glargine to reduce cholesterol, triglycerides (similar with ORIGIN trial)
- No trials or results are available on oxidative stress and inflammation in nondiabetic subjects if effective renoprevention may avoid chronic renal disease (1).

Future Prospects:

Future comparative renoprotection studies in non-diabetics sufficiently powered with long duration on investigation of renal outcome are needed. The non-proteinuric pathway will define better the progressive renal function loss with no or negligible albuminuria in diabetic kidney disease. The option of lifestyle modification, exercise, behavior, attitude, healthy foods, environment, socio-economic uplift measures needs attention and specific government policies.

IV. Conclusion

During the last decade, renal risk factors and pathophysiological mechanisms of diabetic kidney disease were major focus to design treatment strategies to reduce diabetic kidney disease risk in patients without type 2 diabetes. We highlighted less known glucose independent risk factors such as obesity, glomerular hyperfiltration, albuminuria, and dyslipidaemia to prevent chronic kidney disease in patients without type 2 diabetes. Present study serves the purpose to explore multifactorial treatment strategies, substantial residual renal risk remains or therapeutic strategies. Several antihyperglycaemic pleiotropic actions are identified to reduce the renal risk factors in nondiabetic subjects, possibly useful in clinical care. Exploitation of these benefits may add clinical value in the reduction of renal and cardiovascular risk in the near future. However, large and long-term randomised trials will answer whether these off-target actions affect outcome in glucose independent subjects at risk of hypertension and cardiac disease.

Reference

[1]. Muskiet MHA, Tonneijck L, Smits MM, Kramer MHH, Heerspink HJL, van Raalte DH. Pleiotropic eff ects of type 2 diabetes management strategies on renal risk factors. *Lancet Diabetes Endocrinol* 2015; 3: 367–81.

[2]. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001; 414: 782-7.

[3]. De Fronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and alterosclerotic cardiovascular disease. *Diabetes Care* 1991;14:173-94.

[4]. Tschoepe D, Roesen P, Schwippert B, Gries FA. Platelets in diabetes: the role in hemostatic regulation in atherosclerosis. Semin Thromb Haemost 1993;19:122-8.

[5]. Tschoepe D. Langer E, Schauseil S, Rosen P, Kaufmann L, Gries FA. Increased platelet volume—sign of impaired thrombopoiesis in diabetes mellitus. *Klin Wochenschr* 1989;67:253-9.

[6]. Wong T, Pedvis L., Frojmovic M. Platelet size affects both micro- and macro-aggregation: contributions of platelet number, volume fraction, and cell surface. *Thromb Haemost* 1989; 62: 733-41.

[7]. Martyn CN, Mathews DM, Popp-Snijders C, Tucker J, Ewing DJ, Clarke BF. Fffects of sorbinil treatment on erythrocytes and platelets of persons with diabetes. *Diabetes Care* 1986; 9: 36-9.

[8]. Maiti R, Agarawal NK. Atherosclerosis in diabetes mellitus: role of inflammation. *Indian J Med Sci* 2007;61:292-306.

[9]. Goldberg IJ. Clinical review 124: Diabetic dyslipidemia: causes and consequences. J Clin Endocrinol Metab 2001;86:207-71.

[10]. Watala C, Basili S, Falco A, Davi G. Platelet activation in type 2 diabetes mellitus. *J Thromb Haemost* 2004;120:21-8.

[11]. Brownlee M, Cerami A, Vlassara H, Advanced products of nonenzymatic glycosylation and the pathogenesis of diabetic vascular disease. *Diabetes Metab* Rev 1988: 4; 437-51.

[12]. Rashid M, Verhoeven AJM, Mulder MT, Timman R, van Beek-Nieuwland Y, Athumani AA, Zandbergen AAM, van der Wiel HE, Sijbrands EJG, Berk KA. Use of monomeric and oligomeric flavanols in the dietary management of patients with type 2 diabetes mellitus and microalbuminuria (FLAVA trial): study protocol for a randomized controlled trial. *Trials*. 2018; 16;19(1):379.

[13]. Tonneijck L, Muskiet MHA, Smits MM, Bjornstad P, Kramer MHH, Diamant M, Hoorn EJ, Joles JA, van Raalte DH. Effect of immediate and prolonged GLP-1 receptor agonist administration on uric acid and kidney clearance: Post-hoc analyses of four clinical trials. *Diabetes Obes Metab*. 2018;20(5):1235-1245.

i. ----------

Rajiv Kumar Ranjan. "Feasibility of Platelet Indices as Possible Biomarkers in Evaluation of Initial Vascular Risks in Non-Diabetic Subjects.". IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 1, 2019, pp 42-48.