Albuminuria in prediabetes: time to intervene?

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Prediabetes is a metabolic disorder defined by either isolated impaired fasting glucose (IFG) or isolated Impairment in the prandial or random state glycemia or a combination of the two. The definition is not precise as IFG is also an indication of IGT in literal sense. The preferred definition is IGT in the fasting state or non-fasting state. The broad term prediabetes encompasses all intermediate range hyperglycemia between normal and diabetes.

At least 300 million people in the world have the disorder prediabetes [1]. It has attained clinical significance because of the epidemiological association with macrovascular disease and neuropathy and more importantly progression to diabetes. Atherogenic lipid profiles are reported in this state [2, 3]. Lipids worsen before manifest albuminuria, i.e., increasing ACR (albumin/creatinine ratio) even when within normal range in diabetics. Increasing ACR portends worsening lipids which has been reported recently [4].

The report of Nam et al., in the current issue of *Endocrine* goes one step further and shows albuminuria and abnormal lipids early in the prediabetes state of IFG [5]. The authors studied a large population with IFG and compared the data with those having normal fasting glucose. The strength of the study is the sample size and comes from a national survey. The authors followed standard protocols. Data on the diseases and drugs that affect the reported parameters are missing. It is probable that

these effects may be nullified because of the large sample size. They report an increase in atherogenic lipids with microalbuminuria in women.

We have previously reported high cholesterol and triglyceride concentrations in diabetics with proteinuria compared with those without proteinuria but with similar glycated hemoglobin levels in a cross-sectional study. Gender differences were apparent with manifest proteinuria. Women had much worse lipid profile with proteinuria [6]. The results are now replicated in IFG in this larger sample.

The cause effect relation to lipids is complex. Once proteinuria develops, the positive correlation seen between glycated hemoglobin and each of total cholesterol and triglycerides gets weaker or disappears [6]. This means that the very presence of manifest nephropathy influences the changes in lipid concentrations independently than would have been by glycemic control alone.

The components of the metabolic syndrome comprise of prediabetes, dyslipidemias, and microalbuminuria in addition to obesity and hypertension. Insulin resistance is seen at cellular level that in turn leads to hyperinsulinemia which is seen in prediabetes as well as metabolic syndrome. There are differences in the mechanism of hyperglycemia and insulin resistance in IFG and IGT [7, 8]. In subjects with IFG alone, there is a diminished first phase insulin response, while in IGT there is impairment of beta cell function. Reduced hepatic sensitivity is seen early in IFG. There is a well described association of microalbuminuria and components of the metabolic syndrome. A J-shaped association exists between BMI and albuminuria as shown in a large population ($n = 118314$) study [9]. In the current study, the subjects with IFG have higher BMIs. It is hypothetical to say that microalbuminuria and prediabetes are the insults from a common agent. Whether diabetic or non-diabetic, there is sufficient evidence

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confirming higher cardiovascular mortality in subjects with microalbuminuria [10–12].

What does this data mean? Let us compare with another endocrine disorder—subclinical hypothyroidism. Two decades ago, there was paucity of data on its significance. We have seen an explosion of information indicating the presence of dyslipidemias, altered bone density, and cardiovascular risk to mention a few. Currently, prediabetic state is paid great attention in view of the high public health burden thereupon in the coming years.

Intervention studies in prediabetes and diabetes consistently showed benefits in arresting progression or reversal to normoglycemia using various strategies. Diet and physical activity [13], acarbose [14], tolbutamide [15], metformin [16], and orlistat [17] have all been shown to be beneficial. HOPE and Micro-Hope data show the benefits on hyperglycemia from the use of ACE inhibition [10].

What should we do now having accumulated the literature on prediabetes when confronted a person with persistent albuminuria and dyslipidemias in the clinic? Now we know, with prediabetes there is a conglomeration of other risk factors. Prediabetes is defined as a condition and not as a disease entity, but this does not mean it is a benign process which one can passively wait and watch. The most benefited subjects in the Diabetes Prevention Program were the young and the obese [8] suggesting that early intervention yields positive outcomes.

We are still at cross roads with observational data not translated to intervention-based outcomes. Until, clear evidence-based data supports clinical decisions, one is obliged to present the facts to their high-risk subjects and initiate interventions. My practice is to obtain an informed consent and intervene proactively once non-pharmacological management fails. ACE inhibitors are my first choice and I will postpone using statins and pursue dietary interventions in the first instance. Statins have of late got the reputation of worsening glycemia with progression to diabetes. Their benefit to reduce cardiovascular morbidity and mortality events is strong, and therefore, this should not infringe our decision in moderate to high cardiovascular risk patients.

With advancing data capture methods, pooling, meta-analysis, it is only time before guidelines evolve to facilitate our impetus to obtain better outcomes in these pre-clinical disorders.

Conflict of interest None.

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