3. LITERATURE REVIEWS

Investigations on urinary enzymes and microalbumin to prognose and monitor diabetic nephropathy have been reported and can be summarized as follows :

Nakamura S, *et al.*(1991) determined that urinary alanine aminopeptidase (AAP), microalbuminuria and NAG could be used as an early marker of diabetic nephropathy. In the same year, Schneider RE, *et al.*(1991) concluded that in patients with mild essential hypertension, serum NAG activity was elevated where as urinary NAG activity was not and serum NAG was normalized by effective antihypertensive treatment. In 1992, Asami T, *et al.* suggested that in early phase of IDDM, microalbuminuria is preceded by elevation in urinary NAG and beta-2-microglobulin levels and ketone bodies have deleterious effects on renal tubular cells. Skrha J, *et al* (1993), also reported that dynamic changes of the NAG serum activity along with albuminuria can serve as biochemical markers of developing microangiopathy, the manifestation of which is hastened by deteriorated compensation of diabetics. Widstam AU, *et al.* (1992) suggested that early albuminuria in IDDM is of both glomerular and tubular origins. The hyperfiltration increased with the duration of the disease resulting of albumin excretion. In 1993, Ikenaga H, *et al.* evaluated that the excretion of NAG and gamma glutamyl transpeptidase had a higher degree of correlation with glycemic control and renal function than that of dipeptidyl aminopeptidase IV, alanine aminopeptidase and alkaline phosphatase. In the same year, Kanauchi M, *et al.* concluded that microalbuminuria in NIDDM indicated the early morphological changes of glomerular lesions. Wu JT, 1993 also reviewed that clinical complications

associated with diabetes are most likely the consequence of hyperglycemia *via* both altered metabolic pathways and non-enzymatic glycation of proteins. The Amadori product of non-enzymatic glycation will further cross-link with other proteins to form advanced glycosylation end products (AGEs). The uptake of AGEs by receptors on macrophages, endothelial cells and platelets are major reason for the development of various clinical complications in diabetes. Several markers have been identified for the screening, diagnosis and monitoring of the disease. Autoantibodies against beta cells are the best marker for mass screening and for early detection of diabetes type I. In addition to glycated hemoglobin, AGEs and blood glycated proteins of various half-lives, HbA_{1C} and fructosamine could be used for monitoring of glycemic control. The most interesting findings in diabetic markers could be AGEs, which can be assayed by either radioreceptor or immunoassays in blood and tissues. In 1994, Itoh Y, *et al.* found that NAG isoenzyme-B (NAG-B) values are markedly high in the semen which can be contaminated in urine during urination. The clinical significance of NAG-B and total NAG enzymatic activity as a renal tubular marker should be carefully evaluated when analyzing urine from males of reproductive stage. In the same year, Mocan Z, e*t al.* concluded that measurement of urinary NAG activity may be a good indicator in early diagnosis of diabetic nephropathy. The mean urinary NAG level in diabetic group was higher than that of the control group ($p<0.01$). It was observed that NAG activity begins to rise in the third year of NIDDM, makes a plateau between 3-10 years, and rapidly increased after the 10th year. The mean NAG activity in patients with early glomerular hyperfiltration was significantly higher than those without early hyperfiltration and control group ($p<0.05$). In 1995, Lorini R, *et al* had

demonstrated an increase rate of urinary NAG excretion in young IDDM patients, particularly in those with microangiopathic complications. No correlation was observed between NAG/creatinine ratio levels and age, duration of disease, pubertal stage, body mass index, fasting blood sugar. The patients with one or more complications did show NAG/creatinine ratio levels significantly higher than those without complications ($p< 0.005$). Jones AP, *et al.*,(1995) concluded that the increment of NAG excretion in diabetes indicated tubular dysfunction or damage before significant change in albumin excretion rate. Yagame M, *et al* (1995) analyzed urinary albumin fractions (μAF) from patients with NIDDM and concluded that detection of μAF migth be useful for the early detection of diabetic nephropathy in NIDDM. Sanchez HMC, *et al.* (1995) concluded that measurement of urinary NAG may be of value in the detection of diabetic nephropathy at a potentially reversible stage if the plasma glucose was taken into account. The diabetics with plasma glucose more than 140 mg/dl had more significant correlation between NAG: creatinine ratio and AER ($p< 0.001$, $r = 0.70$). In the same year, Furuhata N, *et al.*, found that NAG, one of the glycolytic enzymes, is distributed in various tissue cells. Among them, the lysosome in renal proximal tubular cells contains high amount of NAG. Therefore, urinary NAG is used as a marker which reflect the extent of early renal damage. Urinary NAG can be divided according to electrophoretic mobility into three isozymes, pre A, A and B forms. The measurement of urinary NAG isozymes is useful to determine the type and severity of renal , especially tubular disease. Yaqoob M, *et al.*, 1995, suggested that the degree of albuminuria, transferrinuria and leucine aminopeptidase (LAP) excretion in glomerulonephritis (GN) and diabetic nephropathy (DN) were significantly higher than normal. Serum

creatinine was significantly higher in GN than in DN and controls. The results suggested that tubular damage is less marked in microalbuminuric patients with GN than those with DN despite similar degree of glomerular proteinuria.The pattern of tubulopathy is also different in the two groups, indicating differences in the pathogenesis of tubular damage in these two clinical settings. In 1996, Hsiao PH, *et al* concluded that urinary NAG increased in Chinese IDDM children without any clinical evidence of nephropathy correlated with HbA_{1C} level, suggested that there is tubular dysfunction in the early stage of IDDM children even before there is no clinical evidence of nephropathy and urinary NAG that reflect glycemic control in such patients. In 1997, Hirai M, *et al* suggested that urinary albumin to creatinine ratio (Albumin index) and urinary N-acetyl-beta-D-glucosaminidase (NAG) to creatinine ratio (NAG index) in random spot urine samples can be used to predict the early stage of diabetic nephropathy in the elderly NIDDM patients. Albumin index positively correlated with systolic blood pressure, duration of diabetes and HbA_{1C} ($r = 0.18$, 0.35, and 0.18, respectively). NAG index positively correlated with age, duration of diabetes and HbA_{1C} ($r = 0.18$, 0.25, and 0.29 respectively). In 1997, The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus group reviewed the scientific literatures and decided to revise the definition, classification and diagnotic criteria of diabetes. The change of diagnostic criteria is based on current knowledge about the disease and hazard of consequence complications, for example, in one who has fasting blood sugar equal or above 126 mg/dl, glucose tolerance test should be confirmed instead of 140 mg/dl as used before.

Ruston R, *et al.* (1998) reported that markers of renal tubular injury are difficult to interpret in patients with proteinuria. Using a

modified fast protein liquid chromatography technique, the 'A2' isozyme of NAG was predominate at all levels of renal function and in all diagnostic group. Urinary NAG and proteinuria were well correlated at all levels of renal disease, as was NAG 'A2' isozyme.