DISCUSSION

CHAPTER-IV

DISCUSSION

The precise nature of the protein-bound carbohydrate abnormality and its relation to diabetes, diabetes complications and 'control' are still not clear.

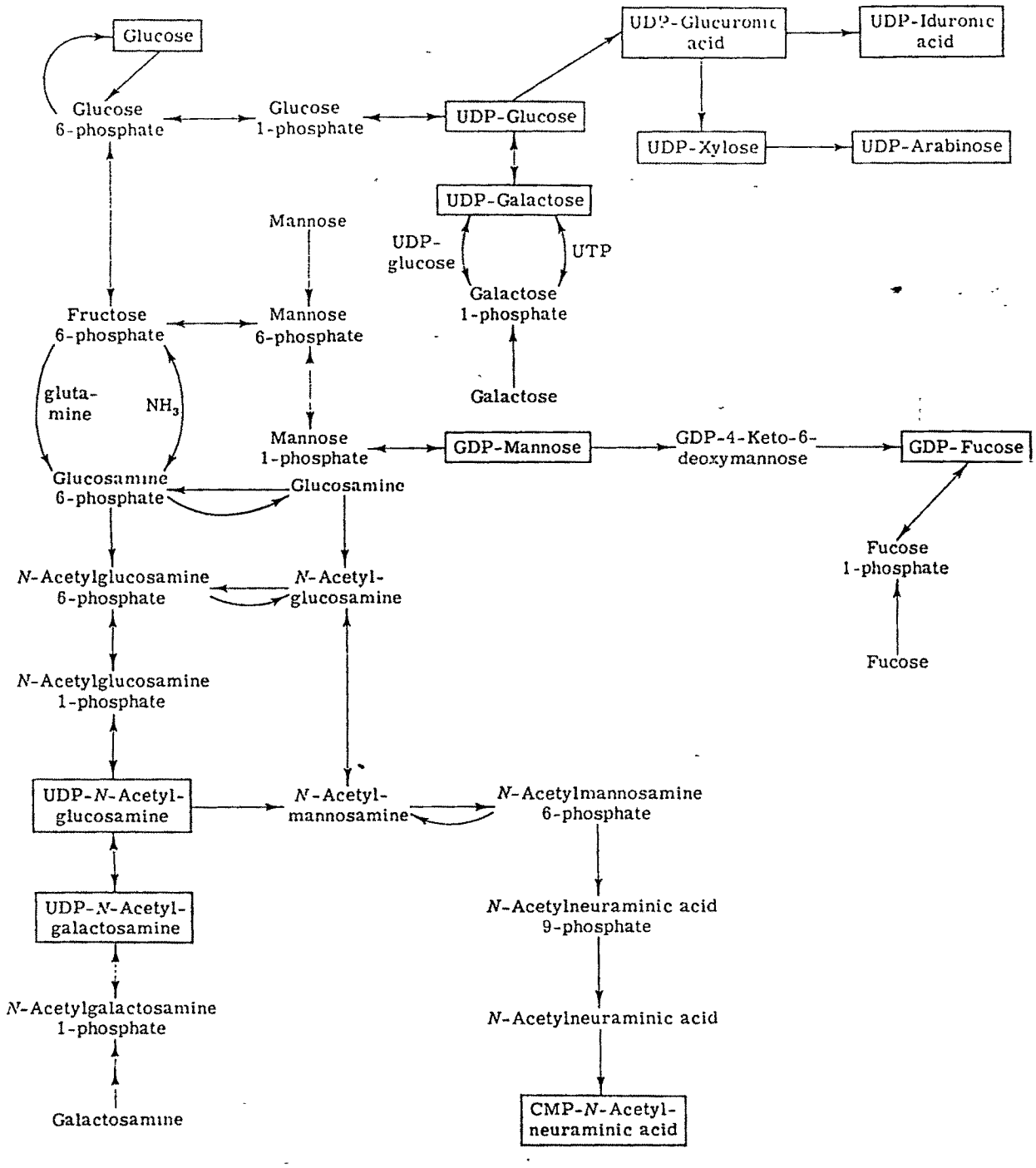
Prior to the analysis of results, a review of the normal metabolism of the plasma proteins is presented.

All the plasma proteins are continuously 'turning over' i.e. they are constantly being utilized or destroyed and replaced by newly synthesized molecules. The turnover of plasma glycoproteins (% replaced / day) is generally more rapid than the turnover of carbohydrate-poor plasma proteins. The possibility exists that the carbohydrate moiety of the plasma glycoproteins might turnover independently of the protein moiety. This would involve the removal of carbohydrate from the protein with subsequent re-addition, perhaps at another site. However, there is no evidence for this kind of carbohydrate transport function of any of the plasma glycoproteins.

Most of the circulating plasma glycoproteins, with the exception of immunolglobulins, are synthesized in the liver (Miller and Bale, 1954; Shetlar, 1961; Robinson et al, 1964; Bekesi and Winzler, 1967). However, there is evidence that circulating glycoproteins may be released from extrahepatic tissues, and that injury may accelerate this release (Catchpole, 1950; Murray and Connell, 1960; Miller, 1964; Molner et al , 1965). The oligosaccharides of the plasma glycoproteins are linked to protein through L-Asparagine-N-acetyl-D-glucosamine (Schachter H., 1974). Asparagine-N-acetyl-D-glucosamine type oligosaccharide have a core containing D-mannose and N-acetyl-D-glucosamine. The monosaccharide components of these oligosaccharides are L-fucose, sialic acid, D-galactose, D-mannose, N-acetylglucosamine and N-acetylgalactosamine. As shown in Figure-8, D-glucose is the major in vivo source of the monosaccharide components of mammalian glycoproteins. D-galactose, D-mannose, D-glucosamine and D-galactosamine from the diet or from glycoprotein catabolism can also enter the metabolic scheme and undergo conversion to other monosaccharides (Schachter H., 1978).

FIGURE-8

BIOSYNTHETIC SCHEME FOR THE MONOSACCHARIDE SUGARS FROM D-GLUCOSE



Adopted from Schachter, H. (1978)

Leloir (1951) and Caputto et al (1949, 1950) found that UDP-D-Glucose played an essential role in the inter-conversion of glucose and galactose, and many similar inter-conversion reactions take place (Feingold, 1972).

Unlike such monosaccharides as glucose, galactose, mannose, glucosamine and galactosamine; fucose is not converted to other monosaccharides (Coffey et al , 1964; Bekesi and Winzler, 1967; Sturgess et al, 1973).

Nucleotide sugars play a major role not only in the inter-conversion of monosaccharides but also in the biosynthesis of the glucosidic linkage (Leloir, 1972). In many cases nucleotide sugars appear to be the immediate precursors of protein-bound carbohydrates.

In secretory glycoproteins, it is evident by tracer studies that the carbohydrate incorporation into growing glycoproteins occurs within the endoplasmic reticulum (rough and smooth surface) and golgi apparatus, after release of nascent polypeptide from membrane-bound polyribosomes. Studies using tracers indicate that sialic acid, galactose and fucose are added

to glycoproteins within the golgi apparatus as the terminal events in the biosynthetic process (Schachter, 1974; a,b).

Glycosyltransferases are enzymes which catalyze the transfer of monosaccharide and oligosaccharide from their activated derivatives to suitable acceptor molecules.

The role of carbohydrate moieties, particularly of sugar, sialic acid and galactose in regulating glycoprotein turnover has been described by Ashwell and Morell (1971, 1974). Their work suggests that the function of the sialic acid residue is to determine the circulating life of glycoproteins and that galactose is necessary for recognition of the desialylated glycoproteins by the liver. Although the mechanism of removal of terminal sialic acid in vivo is not known, the presence of sialidase activity in various organs indicate that the enzyme may play an important role in removal of the terminal sialic acid moiety.

The degradation of glycoproteins is mainly intracellular, chiefly by lysosomes of reticuloendothelial cells.

Almost nothing is yet known about the regulatory mechanism which control the rates of plasma glycoprotein synthesis and breakdown.

In the present study the serum glycoprotein levels, as in terms of PBH, PBSA, PBF and PBHA, along with the fasting blood sugar level are studied in diabetes mellitus patients and in those diabetics who have developed cardiac, renal, hypertension and neuromuscular diseases.

The values of PBH, PBSA, PBF, PBHA and blood sugar in normal subjects are presented in Table-3; the mean values with S.D. are shown in Table-9.

The mean PBH values obtained in normal subjects are in agreement with that obtained by Dutt M. et al (1973). The range of PBH values obtained in the present study overlaps with the range of PBH values obtained by Winzler (1955); Mehta N.G., et al (1975); Kennedy A.L. et al (1979) and Ramdeo L.N. (1983).

The difference in mean values probably depends on the method used for estimation. It is observed that the values obtained by the method using

perchloric acid for precipitation of proteins is higher than the methods using ethanol for precipitation.

In the present study, significant correlation is observed between the blood sugar levels and PBH levels in normal subjects ($r = 0.37$; $P < 0.05$).

The average PBSA value obtained in normal subjects is almost similar to the values obtained by Winzler (1955); Dutt M. et al (1973) ; Mehta N.G. et al (1975); Ramdeo L.N. et al (1983) . Lower value is observed by Sharma N.C. et al (1967).

No significant correlation is observed between the blood sugar and PBSA levels ($r = 0.10$; $P > 0.05$). Studies carried out by Crook M.A., et al (1993) also found no relationship of serum sialic acid levels with blood sugar level or with age.

The average value of PBF is also very similar to those obtained by Winzler (1955); Dutt M., et al (1973) ; Mehta N.G., et al (1975) and Ramdeo L.N. et al (1983). Lower mean level is obtained by Sharma N.C., et al (1967).

The PBF level shows good correlation with the blood sugar level ($r = 0.41$; $P < 0.025$) in the present study.

The mean value of PBHA is same as observed by Dutt M., et al (1973) and Mehta N.G., et al (1975), and are in agreement with the values observed by Winzler (1955) and Ramdeo L.N., et al (1983). No significant correlation is observed between PBHA levels and blood sugar levels ($r = 0.06$; $P > 0.05$).

Studies by Bottiger and Sterky (1962) observed that the mean levels of serum glycoproteins are lower in children as compared to the mean levels in adults, and there is continuous elevation in mean levels till the adult age is attained.

The Indian population on the average has slightly high serum glycoprotein values as compared to the American population (Winzler, 1955; Mehta N.G. et al (1975).

The values of PBH, PBSA, PBF, PBHA and BS in diabetes mellitus patients are presented in Table-4; the mean values with S.D. shown in Table-9.

The fasting blood sugar levels in diabetic patients are significantly higher as compared to that of the normal subjects ($P < 0.05$).

Increased blood sugar level is either due to decreased level of insulin or due to decrease in insulin receptors or may be due to insulin resistance. This results into disturbances in the carbohydrate metabolism and also in the general metabolism in the body.

The mean PBH levels in diabetic patients are significantly higher than those observed in normal subjects ($P < 0.05$). Significant correlation is observed between PBH levels and blood sugar levels ($r = 0.36$; $P < 0.05$).

Similar results are observed by studies done by Ejarque, et al (1959); Mehta N.G. (1975) and Kennedy, et al (1979), in diabetic patients. Kennedy et al, (1979) did not observe any correlation of PBH and blood sugar levels. They observed overlapping in the PBH levels between the controls and diabetic patients.

Increase in PBH can be postulated to be due to disturbances in metabolic processes, as reflected by the rise in blood sugar level, and the increase in PBH is related to the rise in blood sugar levels. There is a possibility of increased enzymatic glycosylation during the synthesis of serum proteins in diabetes mellitus (Stark N.J., 1978).

The mean PBSA level in diabetic patients is observed to be slightly lower than that in normal subjects, but this difference is statistically insignificant ($P > 0.05$). No correlation is observed between the PBSA and blood sugar levels in these patients ($r = 0.12$; $P > 0.05$).

Higher level of PBSA is observed by Mehta N.G. (1975) in diabetic patients, but the number of patients studied by him (total three) is very less to arrive at any general conclusion. Significant elevation of serum sialic acid levels is observed by Crook M.A. (1993 a) in non-insulin-dependent diabetes mellitus (NIDDM), but no significant relationship of total sialic acid level is observed with blood sugar, duration of diabetes or age.

Decrease in PBSA can be attributed to the change in the activity of sialidase enzyme in diabetic patients.

The mean PBF level in diabetic patients is observed to be significantly higher as compared with the normal subjects ($P < 0.01$). Significant correlation is observed between the PBF and blood sugar levels in these patients ($r = 0.52$; $P<0.005$).

Protein-bound fucose is synthesized from D-glucose. Increase in blood glucose level results into increased synthesis of other monosaccharides. Possibly the change in activity of fucosyltransferase leads to increased fucose levels in serum. Two glycoprotein fucosyltransferase activities have been described in human serum (Munro and Schachter, 1973; Chou, et al, 1977).

Alternatively, L-fucose and sialic acid, in many secretory glycoproteins are present in inverse relationship (Dishe Z., 1963). This is explained as due to competition for the same site on the acceptor molecule. It has been

demonstrated that occupation of a site by one of these sugar residue may inhibit the entry of the other sugar into neighbouring unoccupied site.

As the sialic acid levels in the present study are observed to be lower in diabetic patients, the corresponding L-fucose levels are increased.

The mean PBHA level in diabetic subjects is significantly higher as compared with the normal subjects. No significant correlation is observed between the PBHA levels and blood sugar levels ($r = 0.18$; $P > 0.05$). Similar result is observed by Mehta N.G. (1975).

Disturbances in the metabolism in the body, as evident by the raised blood sugar level, may lead to increased utilization of blood sugar. This may be resulting into increased synthesis of hexosamines. Also, probably the diet may be influencing the level of hexosamines.

After formulating our hypothesis we have come across a recent review which fully supports our view (McClain and Crook,1996). This review by McClain and Crook (1996) states that hyperglycemia leads to increased hexosamine synthesis. Excess hexosamine flux causes insulin resistance in cultured cells,

tissues and intact animals. The level of activity of the rate-limiting enzyme in hexosamine synthesis, glutamine : fructose-6-phosphate amidotransferase (GFA) is negatively correlated with glucose disposal rates (GDR) (uptake of glucose in the cells) in normal humans. But in NIDDM subjects, the GFA is positively correlated with GDR (Daniels, M.C., et al, 1996).This suggests that the hexosamine pathway might contribute to the underlying cause of insulin resistance.

The values of PBH, PBSA, PBF, PBHA and blood sugar in cardiac complication diabetics are presented in Table-5; the mean values with S.D. are shown in Table-9.

These cardiac patients have significantly higher blood sugar values ($P<0.01$)., indicating disturbances in the metabolic processes.

The mean PBH level in these patients is slightly higher than that in normal subjects. Studies on ischemic heart patients were observed to have higher levels of PBH (Dutt M., et al, 1973; Tandon S.K., et al, 1983). High levels of PBH were observed by Gero, et al (1961) and Tracy, et al (1961), in

patients with atherosclerosis. Mehta N.G. (1975) and Tandon S.K. et al (1983) observed raised levels of PBH in myocardial infarction and congestive cardiac failure patients.

In the present study, the patients are diabetic, undertaking treatment for hyperglycemia, and as a result of this, their glycemic level is being controlled. Control of glycemic level, probably affects the level of PBH in these patients.

It is observed by Boston Collaborative Drug Surveillance Centre (1974) that diminished elevation of blood glycoprotein level correlates with the use of regular insulin, and it also correlates with blood glucose values in normal range (Jonssan and Wales, 1976).

The average level of PBSA in diabetic patients with cardiac diseases is observed to be higher as compared with that of normal subjects, but this rise is statistically insignificant ($P > 0.05$). No significant correlation is observed between PBSA and blood sugar levels ($r = 0.30$; $P > 0.05$).

Studies by Gero et al (1961) and Tracy et al (1961) reported increase in PBSA level in patients with atherosclerosis. Dutt M., et al (1973), Tandon S.K. et al (1983) observed increase in PBSA levels in patients with ischemic heart diseases. Raised level of PBSA was observed by Mehta N.G. (1975) and Tandon S.K., et al (1983) in myocardial infarction patients, but the rise was not observed in congestive cardiac failure patients. Crook M.A., et al (1993 a) observed no significant difference in sialic acid levels in Type I diabetes mellitus patients as compared to the normal subjects. In their study sialic acid levels correlated significantly with serum triglyceride levels. So serum sialic acid levels can be considered to be a risk factor for cardiovascular diseases in general population. Their study found no relationship between the sialic acid levels and age, duration of diabetes, blood pressure, plasma glucose level or insulin dosage. But studies with Type II diabetes mellitus patients (Crook M. A. et al, 1993 a) showed serum total sialic acid levels significantly higher as compared with Type I diabetic patients.

Manson V.A., et al (1987) observed increased plasma sialidase activity in acute myocardial infarction. Hence the change in sialidase activity might be affecting PBSA levels.

The mean PBF level in diabetic patients with cardiac diseases is significantly higher as compared with the normal subjects ($P < 0.05$). No correlation is observed between the PBF and blood sugar levels in these patients ($r = 0.28$; $P > 0.05$).

Increased level of PBF is observed by Dutt M., et al (1973) and Tandon S. K. et al (1983) in ischemic heart disease. Mehta N.G. et al (1975) and Tandon S. K. et al (1983) observed increase in PBF level in myocardial and congestive cardiac failure patients.

The external location of the fucose residue in glycoproteins makes them labile to the exo-L-fucosidases that are present in most higher organisms, and the afucoglycoproteins are usually good acceptors for fucosyl transferases. Hence there is possibility that changes in fucose content of glycoprotein may occur in pathological states (Warren L., et al 1978).

The mean PBHA level in diabetic patients with cardiac diseases is significantly higher as compared with the normal subjects ($P < 0.01$). No significant correlation is observed between the PBHA and blood sugar levels ($r = 0.13$; $P > 0.05$).

Raised level of PBHA is observed by Dutt M., et al (1973) and Tandon, S. K. et al (1983) in ischemic heart disease patients. Similar results were observed by Tandon S.K. et al (1983) and Mehta N.G. (1975) in myocardial infarction patients and Mehta N.G. (1975) observed increased levels in congestive cardiac failure patients. Gero et al (1961) and Tracy et al (1961) reported marked increase in PBHA atherosclerosis patients.

The probable reason for the high levels of PBHA seems to be due to increased synthesis of hexosamines from glucose. Nutritional factors may also be affecting their level.

The values of PBH, PBSA, PBF, PBHA and BS in diabetics with renal diseases are presented in Table-6. The mean values with S.D. shown in Table-9.

The mean blood sugar level in these patients is significantly higher as compared with that of the normal subjects ($P < 0.01$), indicating metabolic disturbances.

The mean PBH level is slightly higher than the level observed in normal subjects. Same values are observed in cardiac complication patients. No correlation between PBH and blood sugar level is observed ($r = 0.23$; $P > 0.05$).

Mehta N.G., et al (1975) observed higher level of PBH in patients with nephrotic syndrome, but the number of cases studied is (only four) very less to arrive at any general conclusion.

These renal complication patients are undertaking treatment and so their glycemic level is being controlled. This probably affects the level of PBH.

The average PBSA level in these patients is slightly higher than in normal subjects, but the difference is insignificant ($P > 0.05$). No relationship is observed between PBSA and blood sugar levels ($r = 0.30$; $P > 0.05$).

Mehta N.G., et al (1975) observed increased level of PBSA in nephrotic syndrome patients, but the number of patients studied is less to arrive at any general conclusion. Crook M., et al (1994) reported higher levels of serum sialic acid in microalbuminuric patients compared to normoalbuminuric patients. Also in patients with clinical proteinuria, the PBSA level is raised. No relationship was observed by them between the levels of sialic acid and age, diabetes duration or creatinine level.

According to Westberg N.G. (1976), decreased sialic acid in diabetic glomeruli basement membrane contributes to increase in glomerular permeability.

There is evidence for a masking effect of the glycoprotein sialic acid in kidney glomerular membranes, on immunoglobulin receptors, and the decrease in sialic acid of the glomerular membrane that is observed in some renal diseases is presumed to be related to immunological injuries to the glomeruli (Chiu J. and Drummond K.N., 1972).

The average PBF level is significantly higher in renal complication diabetics as compared with the normal subjects ($P < 0.01$). No significant correlation is observed between the PBF and blood sugar levels ($r = 0.28$; $P > 0.05$).

Increased level of PBF in nephrotic syndrome patients is observed by Mehta N.G., et al (1975).

Increased PBF level can be due to change in fucosyl transferase activities or it may be due to the presence of asialoglycoproteins that the activity of fucosyl transferase increases.

The average PBHA level in renal complication diabetics is significantly higher ($P < 0.01$) as compared to the normal subjects. Significant correlation is observed between the PBHA and blood sugar levels in these patients ($r = 0.49$; $P < 0.01$).

Raised levels of PBHA can be attributed to increased synthesis of PBHA as the blood sugar level is raised.

The values of PBH, PBSA, PBF, PBHA and BS in diabetic patients with hypertension are presented in Table-7; the mean values with S.D. are shown in Table-9.

The mean blood sugar level in these patients is significantly higher as compared to the normal subjects ($P < 0.01$). Insulin resistance characterizes patients with essential hypertension (Ferrannini E. et al , 1987; Nantila P. et al, 1995).

The mean PBH level is higher in these patients than that observed in normal patients, but this difference is not significant ($P > 0.05$). No significant relationship is observed between PBH and blood sugar levels ($r = 0.07$; $P > 0.05$).

Rise in PBH level in these patients can be attributed to the poor glycemic control as evident by higher blood sugar level.

The mean PBSA level is higher as compared to that of normal subjects, but this rise is not significant ($P > 0.05$). The range of PBSA level overlaps with

that of normal subjects. No correlation is observed between PBSA and blood sugar levels ($r = 0.17$; $P > 0.05$).

Crook M.A., et al (1993 b) observed significant increase in serum sialic acid levels in NIDDM patients with hypertension.

The reason for the rise in PBSA is still obscure and further study is necessary.

The mean PBF level is significantly higher in these patients as compared to the normal subjects ($P < 0.01$), and good correlation is observed between PBF and blood sugar levels ($r = 0.44$; $P < 0.025$).

Increased synthesis of fucose or change in the activity of fucosyl transferase can be attributed for this high level.

The mean PBHA level in hypertensive patients is also significantly higher than that in normal subjects. No significant correlation is observed between PBHA and blood sugar levels ($r = 0.01$; $P > 0.05$).

Raised levels of PBHA can be attributed to increase synthesis from D-glucose.

The values of PBH, PBSA, PBF, PBHA and BS levels in diabetics with neuromuscular disorders are presented in Table-8. The mean values with S.D. are shown in Table-9.

The mean blood sugar level is significantly higher in these patients than that observed in normal subjects ($P < 0.05$), suggesting metabolic disturbances.

The mean PBH level is lower in these patients than that observed in normal subjects, but this change is insignificant ($P > 0.05$). No significant relationship is observed between PBH and blood sugar levels in these patients ($r = 0.28$; $P > 0.05$).

The decrease in PBH levels may be due to decreased synthesis of hexoses from glucose. because the glucose is utilized in polyol pathway. In polyol pathway the enzyme aldose reductase reduces glucose to form sorbitol. The sorbitol is then oxidized to fructose, by the enzyme sorbitol dehydrogenase.

Aldose reductase has a high Km for glucose and therefore this pathway is quantitatively important during hyperglycemia. It is known that in diabetic animals the sorbitol content of lens, nerve and glomerulus is elevated (Gabbay K.H., 1973; Heath H.H., 1976; Winegrad A.I., et al, 1973; Malona J.I. et al, 1979) causing injuries to these tissues. The study of Sredy J. et al (1991) on diabetic rats observed that sorbitol accumulated in cranial nerves, brain and retina. Administration of aldose reductase inhibitor (tolrestat) normalized polyol levels.

It is postulated that increased sorbitol level may play a role in the pathogenesis of peripheral neuropathy (Gabbay K.H., 1973; Winegrad A.I. et al , 1971; Ludvigson M.A., 1980; Sredy J., et al, 1991).

The mean PBSA level is significantly higher as compared with the normal subjects ($P < 0.05$). No correlation is observed between PBSA and blood sugar levels ($r = 0.38$; $P > 0.05$).

Study by Andrew and Appel (1973) showed increased muscle membrane sialic acid level, in contact with extracellular space, in response to

denervation. The significance of increased sialic acid concentration is not known. Their study indicates that sialic acid increased in membrane with Na^+ , K^+ , (Mg^{++}) ATPase activity and in contact with the extracellular space. So it is unlikely that the primary effect is on its synthesis in sarcoplasmic reticulum. The rise in sialic acid may relate to the altered surface membrane properties associated with denervation.

It is observed by regional studies that no particular enrichment of glycoprotein sialyltransferase occurs in synapse areas (Van den Eijnden and Van Dijk, 1975).

Two distinct forms of neuraminidases, lysosomal and soluble have been shown to be present in rat liver and in brain (Carubelli and Tulsiani, 1971). Role of soluble neuraminidase is not known, but the role of the enzyme in lysosomes appears to be the removal of terminal sialic acid from glycoproteins (Mahadevan, et al, 1967, 1969).

Experiments by Ohman (1971) suggested a complex distribution of human brain neuraminidase, in that 53-77% of recovered neuraminidase was found

in the synaptosomal fraction. He explained that the neuraminidase is bound to the limiting membrane structure of nerve endings; the neuraminidase is primarily located in low density lysosomes, and the enzyme occurs mainly in lysosomes primarily located in the nerve endings trapped during the formation of synaptosomes.

Hence the rise in PBSA can be attributed to the activity of neuraminidase, but further detail study is required to be done.

The average PBF level is found to be significantly higher in these patients as compared to that in normal subjects ($P < 0.01$). No correlation is observed between PBF and blood sugar levels ($r = 0.13$; $P > 0.05$).

The work of Conchie and Hay (1963) suggested that α-fucosidase is a lysosomal enzyme. But the inability of mammalian α-fucosidase to cleave fucosyl residues from intact glycoproteins, requires further investigations.

It is stated that the levels of PBSA and PBF in plasma are in inverse relationship (Dishe Z., 1963). But in the present study, in neuromuscular

disorder patients, the levels of both the PBSA and PBF, are increased. This can be explained due to the release of plasma membrane sialic acid by the action of neuraminidase. Further study in this aspect is still necessary.

The average PBHA level is found to be significantly higher in neuromuscular disorder diabetics as compared to that of normal subjects ($P < 0.01$). No correlation is observed between the PBHA and blood sugar levels ($r = 0.02$; $P > 0.05$).

Rise in PBHA can be attributed to increased synthesis of glutamine from ammonia, formed in the nervous tissue, and the amino acid glutamate. Increased level of glutamine may lead to increased synthesis of hexosamines, coupled with the rise in activity of the enzyme glutamine : Fructose-6-Phosphate amidotransferase.

Total Protein-Bound Carbohydrate (PB-CHO)

Considering the level of total protein-bound carbohydrate, obtained by the summation of the levels of all the individual protein-bound sugars, it is

observed in the present study that the levels of total PB-CHO is higher in diabetic patients and also in all patients suffering from its complications.

Results of the present study are in agreement with the studies of Bierry H., et al (1921); Ejarque, et al (1959); Warren S., et al (1966) and McMillan D.E. (1970).

It is suggested that elevation in total PB-CHO above the normal level reflects process of tissue destruction (Seibert F.B., et al , 1947). This view is supported by the observation that more serum glycoprotein-carbohydrate is found in venous blood than in arterial blood (Bierry H., 1914; Lustig B., et al , 1937).

It is also proposed that the serum glycoproteins may arise as a result of the depolymerization of the ground substance of the connective tissue with the release of solubilized components into the circulation (Catchepole H.R., 1950).

According to Dishe and Osnos (1950) glycoproteins could be liberated preferentially during the course of tissue inflammation or destruction.

Contrary to the above hypothesis, Shetlar et al (1949) suggest that the increase in serum glycoprotein level in disease reflect, in whole or in part, processes associated with tissue proliferation rather than with tissue destruction as observed in prostatic hyperplasia, pregnancy and loss of blood.

It has also been suggested that increased serum glycoproteins may represent systemic response to non-specific stress. As a result of 'stress' tissue damage and increased production of 'acute-phase glycoproteins' occurs (Kennedy et al., 1979; Crook, M. A., 1993b).

Experiments on isolated, perfused livers from diabetic and non-diabetic rats, show that the rate of protein secretion in the diabetic liver is only one-third that of non-diabetics; while the glycoprotein production is doubled (Bar-On, et al, 1977).

This may be due to novo synthesis of glycoproteins or due to an excess glycosylation of existing proteins.

It is observed in the present study that the hyperglycemia in diabetic patients correlates with the rise in levels of PBH. As the glycemic level is being brought under control, the level of PBH decreases.

In all diabetics and in all patients with cardiac, renal and hypertension complications, the level of PBSA is low or it overlaps with normal subjects. It is difficult to arrive at any reasoning for this, unless further study is done considering its level with its biosynthetic and degradative pathways.

Significantly high levels of PBF is observed diabetic patients and also in all patients with cardiac, renal, hypertension and neuromuscular disorders. Further elucidation of PBF levels with the activities of exo-L-fucosidases and fucosyltransferases is necessary to understand the underlying cause.

Significantly high levels of PBHA in all patients of diabetes mellitus and in all its complications studied, suggests a route for utilization of glucose as its level is raised in these patients.

It is necessary to study the effects, 'if any' of various drugs prescribed, in different disorders, on the glycoprotein metabolism.

In conclusion, it can be hypothesized from the present study, that the insignificant or low levels of PBSA in all patients, and as confirmed by corresponding rise in PBF, may also result in decrease in plasma membrane PBSA. Since membrane sialic acid acts as cellular markers, particularly in liver, it is probable that this also includes the insulin receptors. So decrease in membrane sialic acid will result in loss of the receptors and lead to decreased insulin action at membranes and thereby cause the derangement in all the metabolic processes in liver.

Further study can guide us in search for the cause of complications, diagnosis and treatment.