STUDY OF THE EFFECT OF DIALYZER REPROCESSING, INTERLEUKIN-1 ON GLUCOSE HOMEOSTASIS IN HEMODIALYSIS PATIENTS

THESIS

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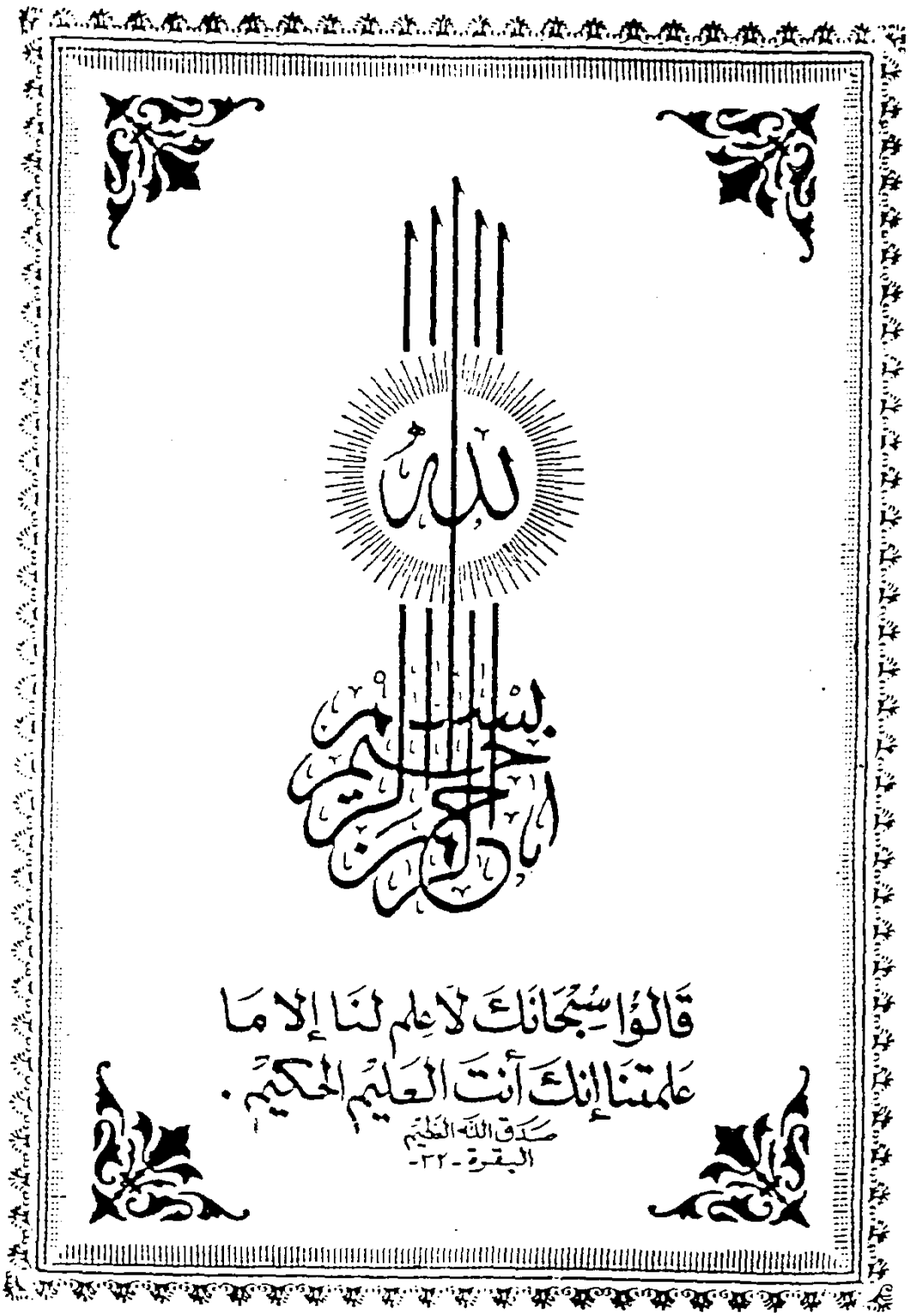

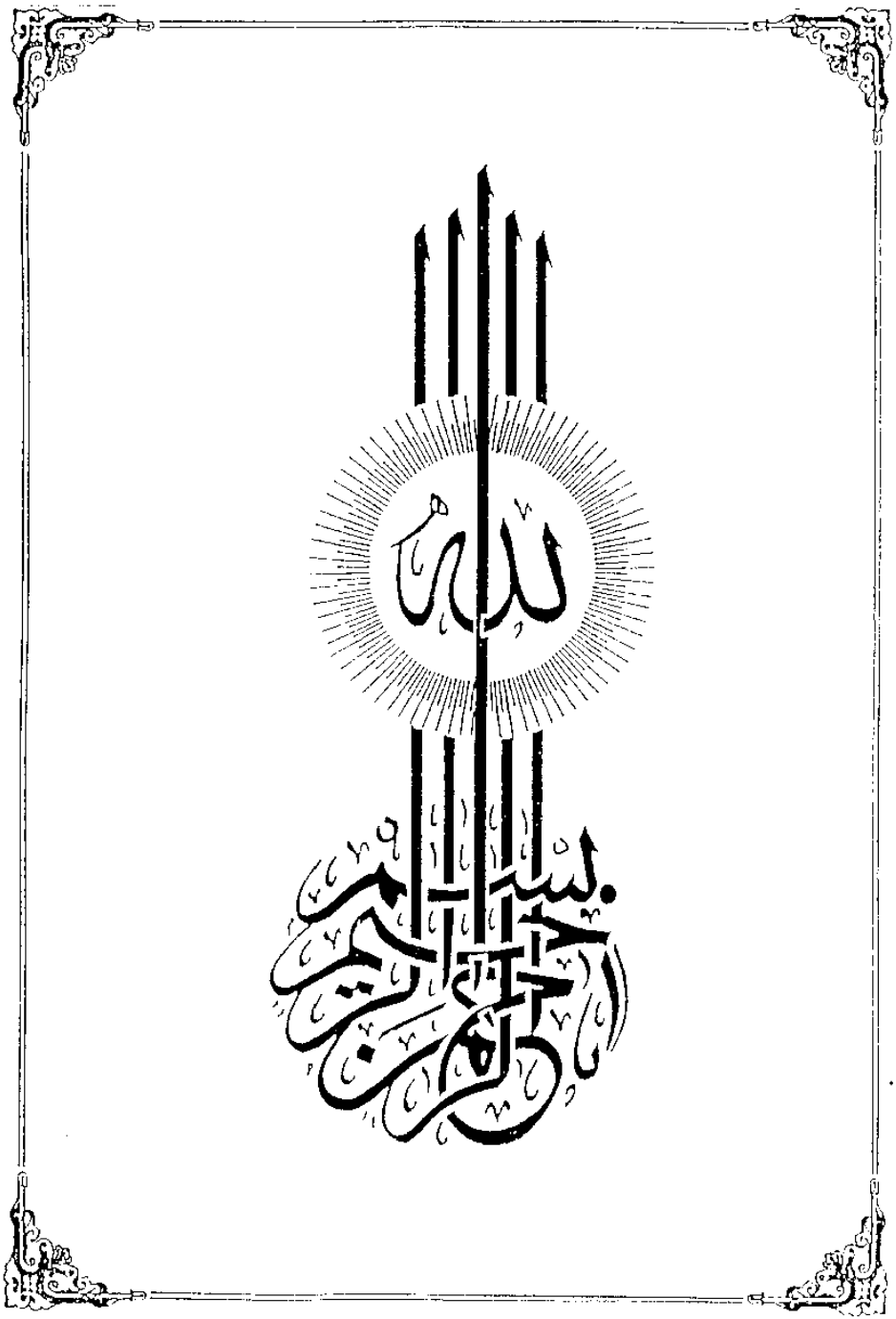

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INTRODUCTION

Blood-membrane biocompatibility is a highly complex problem of interface between non-biological artificial membranes and blood (Andrade, 1981 & Andrade, et al., 1987). Blood-membrane biocompatibility is an important concern that involves the entire hemodialysis treatment (Schulman, et al., 1991). It is not only limited to acute intradialytic reactions as; complement activation, neutropenia, coagulation cascade activation and hypersensitivity reactions but also plays a major role in patient's well being (Leonard, 1984 & Schulman and Hakim, 1991). In the last several years subacute and chronic effects of membrane biocompatibility have been increasingly realized as; dialysis related amyloidosis, increased susceptibility to infections, renal injury, atherosclerosis, protein catabolism and mortality (Ku, et al., 1992 & Cheung, 1994).

During hemodialysis interleukin-1 beta (IL-Iβ) production by monocytes may be influenced by polymers of dialyzer membrane, soluble membrane constituents, activated complement and endotoxins from contaminated dialysate. IL-Iβ can be used as an index for evaluation of membrane biocompatibility (Luger, et al., 1987 & Haeffner-Cavaillon, et al., 1993).

With an expanded knowledge of blood-membrane interaction, several trails attempted to improve biocompatibility trying to improve safety of the patients and patient's quality of life (Schulman and Hakim, 1991).

Reuse of hemodialyzer is one method believed to attenuate blood-membrane interactions, as coating the dialyzer with patient's own plasma proteins during first use will trick the patient's immune system with second use (Chenoweth, et al., 1983 & Dumler, et al., 1987 & Gagnon, et al., 1987 & Vanholder and Ringoir, 1987).

Abnormalities in glucose metabolism are found in 50% of patients with chronic renal failure (De Fronzo, 1983). Hypoglycemia has also been reported as an abnormality in both diabetic and non-diabetic patients during hemodialysis (Schulman, et al., 1991 & Tzamaloukas, 1994). Many mechanisms have been proposed to explain hypoglycemia as reduced insulin catabolism (De Fronzo, 1983), increased insulin production by beta cell to counteract insulin resistance (Mak, 1994), and improvement of insulin binding with decrease of peripheral tissue resistance (Milutinovitc, et al., 1985). Other mechanisms have also been suggested like decrease hepatic glucose production secondary to poor nutrition, anorexia, and the use of glucose free dialysate (Tzamaloukas, 1994).

IL-1 plays an important role in regulation of insulin secretion, it is extremely potent modulator of glucose-induced insulin secretion (Patricia, et al., 1987).

Is IL-Iβ an added mechanism responsible for abnormal glucose homeostasis during hemodialysis and is hypoglycemia a manifestation of bioincompatibility ? So the aim of the present work is to focus on glucose homeostasis in relation to biocompatibility and the role of dialyzer reuse, through attenuation of blood-membrane interaction, to improve hypoglycemia.

Review of Literature

Review of Literature

RENAL DISEASE, INSULIN AND GLUCOSE METABOLISM

Insulin and C-peptide are co-secreted in equimolar concentrations by the pancreatic B-cells (Horwitz, et al. , 1975). C-peptide, in contrast to insulin, is hardly extracted by the liver (Polonsky, et al., 1983 & Bratusch-Marrain, et al., 1984) and therefore, C-peptide concentrations in peripheral venous blood are considered a reliable measure for the insulin production in man (ten-Dam, et al., 1993).

The kidney plays an important role in the metabolism of both C-peptide and insulin, it is responsible for roughly 70% of clearance of C-peptide and for about 30% of the clearance of endogenous insulin (Katz and Rubenstein, 1973). Studies on the renal handling of insulin in both man and rat have shown that renal insulin clearance takes place via two pathways : 1) glomerular filtration followed by almost complete reabsorption of filtered insulin by proximal tubular cells and 2) direct uptake of insulin by tubular cells from the peritubular circulation. For the renal clearance of C-peptide similar routs have been suggested (Katz and Rubenstein, 1973 & Rabkin, et al., 1978).

Renal diseases are often associated with abnormalities in insulin sensitivity and glucose tolerance. The presence of impaired glucose metabolism as evidenced by fasting hyperglycemia and abnormal oral (OGTT) or intravenous (IVGTT) glucose tolerance tests in patients with chronic renal failure has long been recognized. The exact mechanisms underlying the derangements in glucose metabolism are not fully elucidated (De Fronzo, 1983). Some of the features of glucose metabolism in uremia are listed in tab. (1). Although these abnormalities are seldom life threatening situations, their potential pathogenetic implications are significant. Nutritional, metabolic and cardiovascular complications of renal diseases may be consequences of abnormal insulin action (Mak and De Fronzo, 1992).

Tab. (1). Features of glucose metabolism in uremia

* Fasting hyperglycemia.
* Normal fasting blood glucose .
* Spontaneous hypoglycemia .
* Hyperinsulinemia.
*Normal, increased or decreased insulin secretion in response to glucose load.
* Reduced peripheral insulin sensitivity to insulin action .
* Reduced degradation of insulin.
*Decreased requirement for insulin by patients with diabetes mellitus and uremia.

(Mak, 1994).

The glucose intolerance that regularly accompanies uremia has two components 1] Peripheral resistance to the action of insulin. 2] Inhibition of insulin secretion in response to hyperglycemia (Mak,1992c).

Insulin Resistance In Chronic Renal Failure

Reduced tissue sensitivity to the hypoglycemic action of insulin is present almost universally in patients with moderate to sever chronic renal failure (Mak, et al., 1983 & Mak, 1989 & Mak and De Fronzo, 1992). Early evidence includes increased fasting plasma insulin concentrations with normal fasting glucose values, delayed and impaired decline in the plasma glucose concentration in response to intravenous insulin administration and decreased action of insulin to enhance glucose uptake using the forearm perfusion technique (De Fronzo, et al., 1973).

A higher proportion of proinsulin, which is biologically less active than insulin, may account for the elevated immunoreactive insulin concentrations after glucose load and the impaired hypoglycemic action of endogenous immunoreactive insulin in

chronic renal failure. However , this can not account for the tissue insensitivity in uremic patients to exogenous insulin (Mak, 1994).

Little change in the metabolic clearance rate of insulin does not occur until GFR has decreased to less than 15-20 mL/min. This reduction in insulin degradation accounts for the deceased insulin requirement frequently observed in diabetics who developed progressive renal insufficiency (De Fronzo, 1983). Impaired degradation of insulin in non-renal tissues (liver and muscle) also contributes to the prolonged half-life of insulin (Mak and De Fronzo, 1992). Theoretically, the prolonged half-life of insulin can cause hyperinsulinemia, which in turn can down regulate the insulin receptor and induce insulin resistance. However, hyperinsulinemia is only present in about half of the uremic patients with insulin resistance (Mak, 1989 & Mak and De Fronzo, 1992). Also, insulin receptor binding has been shown to be normal in uremic patients (Smith and De Fronzo, 1982). Thus, neither abnormal synthesis or abnormal catabolism of insulin in chronic renal failure can account for insulin resistance.

Insulin resistance can result from : 1) augmented hepatic glucose production, 2) impaired hepatic glucose uptake, or 3) impaired glucose uptake by peripheral tissues primarily muscle and adipose tissues. Basal hepatic glucose production, measured with tritiated glucose, has been shown to be similar in uremic and age-matched control subjects (De Fronzo, et al., 1981 & Mak and De Fronzo, 1992). Moreover, hyperinsulinemia suppressed hepatic glucose production by 90 - 95% in both uremic and control groups (De Fronzo, et al., 1981). It seems unlikely that neither increased basal hepatic glucose production nor impaired suppression during hyperinsulinemia can account for the insulin resistance.

Studies using forearm perfusion techniques in uremic patients (Westerfelt, 1969 & De Fronzo, et al., 1973), and hindlimb perfusion techniques in uremic rats

(Mondon, et al., 1978), have suggested that the site of insulin resistance is in the muscle tissue. De Fronzo, et al., (1981), documented that insulin-mediated glucose uptake was significantly lower (60%) in uremic patients than in control subjects. This is strongly correlated with the decrease in total body insulin-mediated glucose uptake (56%). Because adipose tissue accounts for the disposal of 1-2% of infused glucose load, the muscle tissue must represent the primary tissue responsible for the insulin resistance in uremic patients (Mak, 1994).

Cellular Basis Of Insulin Resistance

Insulin resistance can be the result of abnormalities in the insulin receptor binding or postreceptor events. Smith and De Fronzo (1982), measured insulin binding to monocytes in uremic patients and found that both the receptor number and affinity were normal. They also noted right shift in insulin-mediated glucose disposal dose-response curve that could not be normalized even at pharmacological serum insulin concentration and concluded that postreceptor defects of insulin action were responsible for insulin resistance. Bak, et al., (1989), studied skeletal muscle biopsies from uremic patients and concluded that neither impaired insulin receptor function nor reduced maximal glycogen synthetase activity was involved in the pathogenesis of insulin resistance in these patients. Friedman, et al., (1991), also studied skeletal muscle from uremic patients and found normal insulin binding, B-subunit autophosphorylation and tyrosine kinase activity. Furthermore, the abundance of insulin sensitivity glucose transporter protein (GLUT4) was normal. It seems that the defects involved in the insulin resistance of uremia involved intracellular glucose metabolism (Mc-Caleb, et al., 1985), generation of chemical mediator or second messengers of insulin action (Folli , et al., 1986). Further studies are needed to clarify these abnormalities.

Pathogenesis Of Insulin Resistance

Factors implicated in the pathogenesis of insulin resistance in chronic renal failure are presented in tab. (2).

Tab.(2). Pathogenesis of insulin resistance in uremia

1) Uremic toxins
2) Exercise tolerance
3) Metabolic acidosis
4) Anaemia.
5) Vitamin D deficiency.

Uremic toxins. De Fronzo, et al., (1978), studied uremic subjects with the insulin clamp technique. Before initiation of hemodialysis, insulin-mediated glucose disposal (insulin sensitivity as measured by the clamp technique), was markedly reduced in uremic subjects compared to control subjects, despite steady state plasma insulin levels that were greater than in control subjects. After hemodialysis for 10 weeks insulin sensitivity improved, although it was still lower than control values. Subsequently, Mak and Chantler (1985), showed that continuous ambulatory peritoneal dialysis (CAPD) was more effective than hemodialysis in normalizing insulin sensitivity. It was postulated that uremic toxins, which were removed more efficiently by CAPD, might be the cause of the insulin resistance in uremia.

Some evidence indicates that these uremic toxins may be products of protein catabolism. Mak, et al., (1986), studied the effect of protein restriction on insulin sensitivity in a group of uremic adolescents. Before treatment the patients had high blood urea concentrations and were insulin resistant as measured by the clamp technique. Six months after initiation of dietary protein restriction with amino acid and ketoacid supplementation, significant reduction in blood urea concentrations were accompanied by normalization of insulin resistance. This finding was subsequently confirmed by another group of investigators in adult uremic patients (Aparicio et

al.,1989). The improvement in insulin sensitivity in uremic patients by dialysis, and low protein diets suggested that accumulation of dialyzable toxin(s) from protein catabolism may be responsible for insulin resistance in uremia. Mc-Caleb, et al., (1985), have partially purified and characterized a factor from uremic sera that inhibits insulin-mediated glucose disposal in normal rat adipocytes. This factor is a middle molecule (molecular mass between 1,000–2,000 Da) and is specific for uremia (not present in sera from patients with other insulin--resistant states such as obesity and diabetes mellitus). Folli, et al., (1986), further characterized the toxin(s) using cultured rat hepatocytes. They showed that normal rat hepatocytes could be rendered insulin resistant by uremic sera. The defect seemed to be in the generation of chemical mediator or second messenger of insulin action, whereas the structure, autophosphorylation and tyrosine kinase activity of the receptor were not impaired.

Exercise tolerance. Patients with uremia have low work capacity. Their low exercise tolerance may contribute to their endocrine--metabolic abnormalities. Goldberg, et al., (1980), showed that moderate endurance training programs improved both the exercise tolerance and insulin sensitivity in patients on hemodialysis. The magnitude of the improvement in insulin sensitivity was greater than would have been anticipated because of changes in diet or body composition, furthermore, the return of insulin resistance toward pretraining level in patients who stopped training suggested that the training effect was primary. Furthermore, Davis, et al., (1987), showed that exercise training increased insulin sensitivity and responsiveness of muscle glucose uptake and glycolytic utilization in rat with chronic renal failure and controls. These latter investigators concluded that the defect in insulin-mediated glucose metabolism in muscle from rats with chronic renal failure could be partially but not totally corrected by exercise training.