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Insulin resistance in chronic kidney disease: Is it a hepatic Cushings?

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Insulin resistance and associated metabolic consequences are almost universal in chronic kidney disease (CKD) and are independently associated with increased cardiovascular mortality. Furthermore, mortality among patients treated with dialysis is higher in those with more severe insulin resistance. Despite this, the mechanisms responsible for the onset of insulin resistance in CKD are unclear. 11β-hydroxysteroid dehydrogenase type 1 (11betaHSD1) catalyses intra-cellular regeneration of active glucocorticoids, promoting insulin resistance in liver and other metabolic tissues. Experimental murine models of CKD demonstrate early insulin resistance, alongside high 11betaHSD1 mRNA and protein in hepatic and adipose tissue, together with increased activity. This is associated with intrahepatic but not circulating glucocorticoid excess, and increased hepatic gluconeogenesis and lipogenesis. Oral administration of the 11betaHSD1 inhibitor carbenoxolone improves glucose tolerance and insulin sensitivity, improved insulin signalling and reduced hepatic expression of gluconeogenic and lipogenic genes. Furthermore, uremic 11betaHSD1-/- mice and rats treated with a specific inhibitor are protected from metabolic disturbances. Therefore, data suggest that local hepatic Cushings syndrome because of elevated 11betaHSD1 is an important contributor to early insulin resistance and dyslipidemia in uremia. Specific 11betaHSD1 inhibitors may represent a novel therapeutic approach for management of insulin resistance in patients with CKD.

Biography

Muhammad Magdi Yaqoob is currently Professor and Academic Director of the Renal Unit at Barts Health NHS Trust and William Harvey Research Institute. After qualifying from Karachi, Pakistan, he completed his general and specialist renal training in UK and USA. He is the head of Translational Renal Research laoboratory at the William Harvey Research Institute UK. He has published more than 200 peer reviewed publications in international journals and contributed seven chapters in medical text books. His research interests include uremic cardiovascular disease, diabetic kidney disease, acute kidney injury, erythropoietin resistance and pharmacogenomics in renal transplantation.

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