Endocrinology & Metabolic Syndrome
ISSN: 2161-1017

Horita et al. Endocrinol Metabol Syndrome 2011, S:1
DOI: 10.4172/2161-1017.S1-005

Review Article Open Access

Metabolic syndrome and insulin signaling in kidney

Shoko Horita, George Seki*, Hideomi Yamada, Masashi Suzuki, Motonobu Nakamura and Toshiro Fujita

Department of Internal Medicine, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo Tokyo 113-0033, Japan

Abstract

Metabolic syndrome (MetS) is now recognized as a big threat for human health. It has been a problem in developed countries for decades and also emerging similarly in developing countries. It has been also called as "Syndrome X", "Deadly quartet", "Reaven's syndrome". Essentially these are of the same clinical status, in which insulin resistance is the common condition. In such condition hyperinsulinemia occurs, which may have potential influence on other organs and tissues, including kidney – glomeruli and tubules - , cardiovascular systems, liver, muscles. This review will focus on the influence of MetS on the point of insulin resistance and its influence of kidney, especially proximal tubules and glomeruli.

Keywords: Insulin Resistance, Hypertension, Renal Proximal Tubules, Electrogenic Na^+-HCO_3^- Cotransporter (Nbce1)

The history and the definition of metabolic syndrome

The status like MetS was reported as early as in 1920s [1,2]. The word MetS itself was first used by Haller [3]. He mentioned about the risk of atherosclerosis associated with obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia, and steatosis hepatis.

Reaven described that insulin resistance is the key factor of this phenomenon [4]. He proposed that insulin resistance is closely related to impaired glucose tolerance, hyperglycemia, hyperlipidemia and hypertension. He called this as "Syndrome X". Then, Kaplan proposed the idea "Deadly quartet", upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension [5].

WHO first made criteria for MetS in 1999 [6], consisting of obesity, hyperlipidemia, hypertension, hyperglycemia, insulin resistance and albuminuria [6]. Some other criteria have been published later, but it seems to be difficult to adapt the single criterion perfectly to all people, as there are genetic and environmental differences among people.

Metabolic syndrome and insulin resistance, hypertension

The criteria of MetS are still hotly debated [7,8], but insulin resistance is recognized as one of the key factors of MetS. The definitions of the American Association of Clinical Endocrinology (AACE) [9], WHO [6] and the European Group for the study of Insulin Resistance (EGIR) [10] focus on insulin resistance, whereas the widely used definitions such as, the National Cholesterol Education Program Adult Treatment Panel III criteria (NCEP-ATP III) [11], its modified version the American Heart Association / National Heart, Lung, and Blood Institute criteria (AHA/NHLBI) [12,13] and the International Diabetes Federation criteria (IDF) [14] rather focus on waist circumference. Nevertheless, as Reaven described, insulin resistance is related to pathogenesis of hyperglycemia, fatty acid dysregulation, and hypertension [4].

As for salt-sensitive hypertension, the relationship with MetS and insulin resistance has been pointed out. Uzu and colleagues have reported associations between the presence of MetS and salt-sensitive hypertension [15]. In essential hypertension, there are several reports that describe impaired insulin signaling [16-22]. McFarlane and Sechi showed direct correlation between plasma insulin levels and blood pressure in such patients [17,18]. Genetic background is thought to be important in both essential and salt-sensitive hypertension; it has been observed that offspring of hypertensive parents has abnormal glucose metabolism. As the relationship between hyperinsulinemia and hypertension is not seen in secondary hypertension, insulin resistance and hyperinsulinemia may not be consequences of hypertension [18,19].

In human the anti-natriuretic action of insulin is seen [23], which is supportive for the idea that hyperinsulinemia may contribute to the onset of hypertension via sodium retention in the kidney [24,25]. On the other hand insulin itself stimulates nitric oxide (NO) production, which relaxes the vascular tone through the phosphoinositide 3-kinase (PI3K) / Akt pathway [21,26], suggesting that hyperinsulinemia itself may not directly induce hypertension in the absence of insulin resistance [27]. However, in insulin resistance condition, it has been observed that the NO production stimulated by insulin is attenuated [28]. The resultant attenuated vasodilatation by insulin may underlie the onset of hypertension in insulin resistance condition.

In molecular aspects, there are some types of inherited hypertensions, e.g. Liddle's syndrome [29] and pseudohypoaldosteronism type II or familial hyperkalemic hypertension (FHH) [30]. Although they never represent as common diseases, the investigations of the mechanism of these diseases have led to clarify novel signal transduction systems that may play important roles in the pathogenesis of MetS and hypertension. Liddle's syndrome is due to mutation in epithelial Na channel (ENaC) in the distal tubule [31], whereas FHH is due to the abnormality in kinases (with-no-lysine [K] kinase; WNK 1~4) [32]. In addition to these distal nephron Na transport systems, however, the Na transport in proximal tubules may be also related to the pathogenesis of hypertension, as will be discussed below.

Insulin effect on renal proximal tubule and sodium transport

Insulin exerts its action on kidney, especially the whole nephron. As to proximal tubule, insulin accumulates in the proximal tubule [33]. In rabbit insulin binds to various segments of nephron [34], whereas insulin accumulates strongest in the proximal tubule of rat nephron [35]. Insulin is delivered to proximal tubule by two ways: by glomerular filtration and subsequent reabsorption from tubular cells,

***Corresponding author:** George Seki, Department of Internal Medicine, Faculty of Medicine, University of Tokyo,7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, Tel: +81-3-3815-5411; Fax: +81-3-5800-8806; E-mail: georgeseki-tky@umin.ac.jp

Received November 01, 2011; **Accepted** November 30, 2011; **Published** December 03, 2011

Citation: Horita S, Seki G, Yamada H, Suzuki M, Nakamura M, et al. (2011) Metabolic syndrome and insulin signaling in kidney. Endocrinol Metabol Syndrome S1:005. doi:10.4172/2161-1017.S1-005

and by diffusion from peritubular capillaries and subsequent binding to insulin receptors [36].

So far it is known that insulin stimulates sodium reabsorption in the proximal tubule [23]. Insulin also stimulates volume absorption in rabbit proximal tubule, via basolateral side [37]. As proximal tubules reabsorb about seventy percents of total sodium filtered from glomeruli, the stimulation of proximal sodium reabsorption by insulin may well contribute to the increase of total fluid volume in the individual, leading to hypertension.

Gesek and Schoolwerth showed that in rat proximal tubule the activity of Na^+-H^+ exchanger type 3 (NHE3) is increased by insulin [38]. As NHE3 plays quite a significant role in the apical side of proximal sodium reabsorption, this effect of insulin is quite important. The cellular mechanism of insulin action was investigated by Lee-Kwon et al. [39,40] and Shiue et al. [41]. It is not still totally clarified but Akt seems to play a critical role in the PI3K mediated translocation of NHE3 into apical membranes of proximal tubular cells.

Ruiz et al. showed that insulin stimulates Na^+-HCO_3^- cotransporter (NBCe1) in the basolateral side of proximal tubule [42]. Na^+-K^+-ATPase also plays a role in the Na^+ reabsorption in the proximal tubule and is a target of insulin stimulation [43, 44].

Difference of insulin signals between organs – tubules and adipose tissues

As described above, insulin has a significant effect on renal proximal tubule, but its mechanism is still under investigation. As for sodium transport we have examined the insulin signal transduction mechanism involving IRS1 and/or IRS2 [45]. In wild-type mice and $IRS1^{-/-}$ mice insulin significantly stimulated Na^+-coupled HCO_3^- absorption but the stimulation was significantly attenuated in $IRS2^{-/-}$ mice. Moreover the Akt phosphorylation induced by insulin stimulation, which might mediate the effect of insulin on proximal absorption, was preserved in $IRS1^{-/-}$ mice but significantly reduced in $IRS2^{-/-}$ mice. In proximal tubule the tyrosine phosphorylation of IRS2 by insulin seems to be more prominent than that of IRS1, consistent with a major role of IRS2 in insulin-mediated transport stimulation in proximal tubule. Signaling defects specific to IRS1 are frequently showed in insulin resistance [46-49]. Our results suggest that the stimulation of proximal tubule transport by insulin may be preserved even in insulin resistance.

In fat tissue, which is one of the common tissues that insulin resistance arises, IRS1 seems to play a major role in the insulin signal transduction. Hotamisligil and colleagues first described that in mice adipose tissue TNF-α plays an important role in the development of insulin resistance [50]. TNF-α induces inflammation, leading to inhibition of IRS1/2 signal transduction pathways [51-53], and may inhibit the insulin signaling through the serine phosphorylation of IRS1 [54]. It is now established that IRS1 is phosphorylated at serine residues by various kinases [51]. These kinases seem to interfere with IRS1 functions, resulting in inhibition of insulin-receptor signaling and alteration in insulin action [55-57].

As described here, IRS2 signaling seems to be prominent in the proximal tubule, whereas IRS1 signaling seems to be major in adipose tissue. This difference in signaling pathways could explain the different responses to insulin between kidney and adipose tissue. Especially, even in insulin resistance, insulin signaling seems to be preserved in the proximal tubule, stimulating sodium and fluid reabsorption followed by hypertension. This may explain one of the important pathogenesis of hypertension under insulin resistance condition.

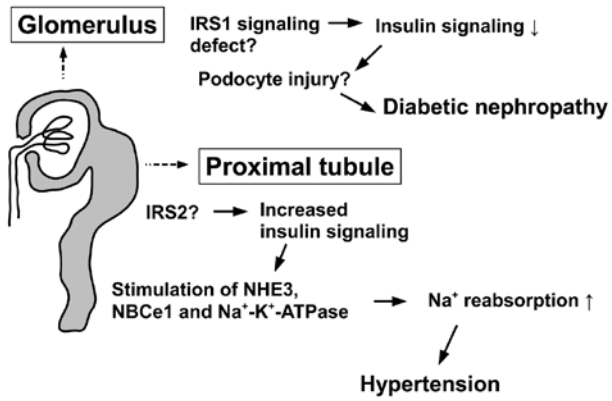

Figure 1: Effects of MetS on insulin signaling in the kidney. In the glomerulus insulin resistance induced by and/or concomitant with MetS leads to the impairment of insulin signaling in the glomerulus. This leads to diabetic nephropathy probably due to podocyte injury. In contrast in the proximal tubule insulin signaling is preserved, and hyperinsulinemia triggers increment of proximal reabsorption and hypertension.

On the contrary in the glomeruli the insulin signal transduction seems to be reduced as in adipose tissue, as will be described in the next chapter.

Insulin effect in animal models: difference between glomeruli and tubules

Several rat models have been used to investigate the insulin effects in MetS condition and the mechanism of insulin resistance. One of the rat models is Otsuka Long-Evans Tokushima Fatty (OLETF) rat [58]. This rat has a defect in cholecystokinin -A (CCK-A) receptor [59], resulting in obesity due to overeating [60]. Compared to its counterpart control rat (Long-Evans Tokushima Otsuka rat; LETO rat), OLETF rat begins accelerated weight gain at 5 weeks of age, leading to about 40% excess of weight than LETO rat. Moreover, OLETF rat develops hyperglycemia and type II diabetes mellitus at about 18 weeks of age, resulting in insulin deficiency after 65 weeks of age [58].

Our group investigated whether the effect of insulin on the proximal tubule of OLETF rats is preserved or not [61]. We also investigated the adipose function under insulin resistant condition in these rats. The stimulation of glucose uptake into adipocytes by insulin was severely impaired in OLETF rats compared to LETO rats, indicating that OLETF rats develop insulin resistance in adipose tissue. In sharp contrast, the stimulation of NBCe1 by insulin was comparable in both rats. In OLETF rats Akt phosphorylation by insulin was preserved in renal cortex tissue but severely reduced in adipocytes. These results suggest that in general obese condition, such as MetS and/or insulin resistance, hyperinsulinemia may contribute to the emergence of hypertension by facilitating renal Na absorption.

In glomeruli the signal transduction pathway by insulin seems to be differently affected from that of proximal tubules, rather as is in adipose tissue. King and colleagues have recently clarified that the responses to insulin in rat models of diabetes and obesity – Zucker lean rats and control SD rats - are different between glomeruli and tubules [62]. In the glomeruli insulin-induced phosphorylation of IRS1, Akt, endothelial nitric oxide synthase (eNOS), and glycogen synthase kinase 3α (GSK3α) were all inhibited in glomeruli but not in the tubules. The defect in glomerular insulin signaling was similar to that in all other vascular tissues when exposed to insulin resistance and diabetes [63,64]. On the other hand, renal tubules seemed to be selectively

protected from developing insulin resistance. This conclusion seems to be consistent with the preserved insulin action on proximal tubule in OLETF rats [61].

One of the organ dysfunction elicited by MetS should be diabetic nephropathy (DN) [65]. The pathogenesis of DN is still under investigation. As to type I diabetes, the presence of insulin resistance seems to be necessary for the onset of DN [66]. Coward and colleagues have shown that the glomerular podocyte plays the key function in insulin signal pathway [67]. They created two types of mice model with podocyte-specific insulin receptor knockout and showed that insulin rapidly and directly signal to the podocyte, and directly and specifically reorganize the actin cytoskeleton of podocytes. It has been known that the main damaged cell type in human DN is podocytes with foot widening [68,69]. Other group showed that the similar knockout mice (podocyte insulin-receptor knockout) developed albuminuria and had histological changes characteristic to DN, e.g. loss of podocyte morphology, and even podocyte apoptosis [70]. As podocyte loss is an important feature of DN that occurs in the relatively early stage and is a good predictor of disease progression [69,71], investigations of the insulin effect on podocyte may help develop the new strategy for prevention and treatment of DN.

Does improvement of insulin resistance ameliorate kidney function?

The relation between MetS and kidney function has been vigorously investigated. Several studies suggest that the improvement of lifestyle and use of drugs may ameliorate kidney function. For example, exendin-4, one of the anti-diabetic drug glucagon-like peptide-1 analogues has been suggested to ameliorate diabetic nephropathy [72]. Other anti-diabetic drug, peroxisome proliferator- activated receptors gamma (PPAR-γ) agonist, was proved to ameliorate mesangial expansion, improve GFR, and reduce albuminuria [73-75]. As for life style it has been shown that in MetS subjects exercise induced improvement in renal function [76]. However, there has been no clear evidence showing direct relation between kidney function and insulin resistance. Further investigations will be required to solve this issue.

Conclusion

MetS is the main life-threatening disorder in developed and some developing countries. It is also a menace to kidney probably due to concomitant insulin resistance and following diabetes and hypertension. The criterion of MetS is still not completely established but insulin resistance is certainly a key factor of MetS.

In insulin resistance condition, the signal transduction pathway of insulin is impaired in most organs and tissues. However, the situation may be different in proximal tubule. In proximal tubules the insulin signaling pathway is probably preserved and, hence, hyperinsulinemia may stimulate proximal transport. The resultant sodium retention, together with the impaired vasodilatation by insulin, may induce hypertension. In contrast, glomerulus may develop insulin resistance like other vascular system. In particular, podocytes seems to be mainly affected by insulin resistance, responsible for the histological change characteristic to DN. Figure 1 summarizes the potential effects of MetS on insulin signaling in the kidney.

To prevent kidney impairment by insulin resistance, two different approaches may be required; for proximal tubules it is necessary to prevent the excessive stimulation of reabsorption by insulin, whereas for glomerulus the prevention of podocyte injury may require the improvement of insulin signaling.

References

1. Joslin E (1921) THE PREVENTION OF DIABETES MELLITUS. JAMA 76:79-84
2. Kylin E (1923) Studies of the hypertension-hyperglycemia-hyperuricemia syndrome. Zentralbl Inn Med 44:105-127 (German)
3. Haller H (1977) [Epidermiology and associated risk factors of hyperlipoproteinemia]. Z Gesamte Inn Med 32: 124-128.
4. Reaven GM (1988) Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 37: 1595-1607.
5. Kaplan NM (1989) The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. Arch Intern Med 149: 1514-1520.
6. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 15: 539-553.
7. Gupta A, Gupta V (2010) Metabolic syndrome: what are the risks for humans? Biosci Trends 4:204-212.
8. Kassi E, Pervanidou P, Kaltsas G, Chrousos G (2011) Metabolic syndrome: definitions and controversies. BMC Med 9:48.
9. Einhorn D, Reaven GM, Cobin RH, Ford E, Ganda OP, et al. (2003) American College of Endocrinology position statement on the insulin resistance syndrome. Endocr Pract 9: 237-252.
10. Balkau B, Charles MA (1999) Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med 16: 442-443.
11. Expert Panel on Detection Ea, and Treatment of High Blood Cholesterol in Adults (2001) Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 285: 2486-2497.
12. Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C (2004) Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 109:433-438.
13. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, et al. (2005) Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 112:2735-2752.
14. Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group (2005) The metabolic syndrome--a new worldwide definition. Lancet 366:1059-1062.
15. Uzu T, Kimura G, Yamauchi A, Kanasaki M, Isshiki K, et al. (2006) Enhanced sodium sensitivity and disturbed circadian rhythm of blood pressure in essential hypertension. J Hypertens 24: 1627-1632.
16. Ferri C, Bellini C, Desideri G, Giuliani E, De Siati L, et al. (1998) Clustering of endothelial markers of vascular damage in human salt-sensitive hypertension: influence of dietary sodium load and depletion. Hypertension 32: 862-868.
17. McFarlane SI, Banerji M, Sowers JR (2001) Insulin resistance and cardiovascular disease. J Clin Endocrinol Metab 86:713-718.
18. Sechi LA, Melis A, Tedde R (1992) Insulin hypersecretion: a distinctive feature between essential and secondary hypertension. Metabolism 41:1261-1266.
19. Sowers JR, Epstein M, Frohlich ED (2001) Diabetes, hypertension, and cardiovascular disease: an update. Hypertension 37:1053-1059.
20. Sowers JR, Haffner S (2002) Treatment of cardiovascular and renal risk factors in the diabetic hypertensive. Hypertension 40:781-788.
21. Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, et al. (1996) Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. J Clin Invest 97:2601-2610.
22. Vecchione C, Colella S, Fratta L, Gentile MT, Selvetella G, et al. (2001) Impaired insulin-like growth factor I vasorelaxant effects in hypertension. Hypertension 37: 1480-1485.
23. DeFronzo RA, Cooke CR, Andres R, Faloona GR, Davis PJ (1975) The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. J Clin Invest 55: 845-855.

24. Natali A, Quinones Galvan A, Santoro D, Pecori N, et al. (1993) Relationship between insulin release, antinatriuresis and hypokalaemia after glucose ingestion in normal and hypertensive man. Clin Sci (Lond) 85:327-335

25. Quinones-Galvan A, Ferrannini E (1997) Renal effects of insulin in man. J Nephrol 10:188-191.

26. Sowers JR (2004) Insulin resistance and hypertension. Am J Physiol Heart Circ Physiol 286: 1597-1602.

27. Hall JE (1993) Hyperinsulinemia: a link between obesity and hypertension? Kidney Int 43:1402-1417.

28. El-Atat FA, Stas SN, McFarlane SI, Sowers JR (2004) The relationship between hyperinsulinemia, hypertension and progressive renal disease. J Am Soc Nephrol 15:2816-2827.

29. Liddle GW, Bledsoe T, Coppage WS 1963 A FAMILIAL RENAL DISORDER SIMULATING PRIMARY ALDOSTERONISM BUT WITH NEGLIGIBLE ALDOSTERONE SECRETION. Transactions of the Association of American Physicians 76:199-213.

30. PAVER WK, PAULINE GJ (1964) HYPERTENSION AND HYPERPOTASSAEMIA WITHOUT RENAL DISEASE IN A YOUNG MALE. Med J Aust 2:305-306.

31. Shimkets RA, Warnock DG, Bositis CM, Nelson-Williams C, Hansson JH, et al. (1994) Liddle's syndrome: heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel. Cell 79: 407-414.

32. Wilson FH, Disse-Nicodeme S, Choate KA, Ishikawa K, Nelson-Williams C, et al. (2001) Human hypertension caused by mutations in WNK kinases. Science 293:1107-1112.

33. Bourdeau JE, Chen ER, Carone FA (1973) Insulin uptake in the renal proximal tubule. Am J Physiol 225:1399-1404.

34. Nakamura R, Emmanouel DS, Katz AI (1983) Insulin binding sites in various segments of the rabbit nephron. J Clin Invest 72:388-392.

35. Butlen D, Vadrot S, Roseau S, Morel F (1988) Insulin receptors along the rat nephron: [125I] insulin binding in microdissected glomeruli and tubules. Pflugers Arch 412:604-612.

36. Rabkin R, Ryan MP, Duckworth WC (1984) The renal metabolism of insulin. Diabetologia 27:351-357.

37. Baum M (1987) Insulin stimulates volume absorption in the rabbit proximal convoluted tubule. J Clin Invest 79:1104-1109.

38. Gesek FA, Schoolwerth AC (1991) Insulin increases Na^+-H^+ exchange activity in proximal tubules from normotensive and hypertensive rats. Am J Physiol 260:F695-703.

39. Lee-Kwon W, Kawano K, Choi JW, Kim JH, Donowitz M (2003) Lysophosphatidic acid stimulates brush border Na^+/H^+ exchanger 3 (NHE3) activity by increasing its exocytosis by an NHE3 kinase A regulatory protein-dependent mechanism. J Biol Chem 278:16494-16501.

40. Lee-Kwon W, Johns DC, Cha B, Cavet M, Park J, et al. (2001) Constitutively active phosphatidylinositol 3-kinase and AKT are sufficient to stimulate the epithelial Na^+/H^+ exchanger 3. J Biol Chem 276:31296-31304.

41. Shiue H, Musch MW, Wang Y, Chang EB, Turner JR (2005) Akt2 phosphorylates ezrin to trigger NHE3 translocation and activation. J Biol Chem 280: 1688-1695.

42. Ruiz OS, Qiu YY, Cardoso LR, Arruda JA (1998) Regulation of the renal Na-HCO3 cotransporter: IX. Modulation by insulin, epidermal growth factor and carbachol. Regul Pept 77:155-161.

43. Taylor Z, Emmanouel DS, Katz AI (1982) Insulin stimulates Na-K-ATPase activity of basolateral renal tubular membranes (abstract), 1982, p 266.

44. Rivera C, Reyes-Santos H, Marinez-Maldonado M (1978) Response of dog renal Na^+, K^+-ATPase to insulin in vitro. Renal Physiol 1:74-83.

45. Zheng Y, Yamada H, Sakamoto K, Horita S, Kunimi M, et al. (2005) Roles of insulin receptor substrates in insulin-induced stimulation of renal proximal bicarbonate absorption. J Am Soc Nephrol 16:2288-2295.

46. Goodyear LJ, Giorgino F, Sherman LA, Carey J, Smith RJ, et al. (1995) Insulin receptor phosphorylation, insulin receptor substrate-1 phosphorylation, and phosphatidylinositol 3-kinase activity are decreased in intact skeletal muscle strips from obese subjects. J Clin Invest 95: 2195-2204.

47. Friedman JE, Ishizuka T, Shao J, Huston L, Highman T, et al. (1999) Impaired glucose transport and insulin receptor tyrosine phosphorylation in skeletal muscle from obese women with gestational diabetes. Diabetes 48:1807-1814.

48. Rondinone CM, Wang LM, Lonnroth P, Wesslau C, Pierce JH, et al. (1997) Insulin receptor substrate (IRS) 1 is reduced and IRS-2 is the main docking protein for phosphatidylinositol 3-kinase in adipocytes from subjects with non-insulin-dependent diabetes mellitus. Proc Natl Acad Sci U S A 94:4171-4175.

49. Carvalho E, Jansson PA, Axelsen M, Eriksson JW, Huang X, et al. (1999) Low cellular IRS 1 gene and protein expression predict insulin resistance and NIDDM. Faseb J 13: 2173-2178.

50. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS (1997) Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature 389: 610-614.

51. Hotamisligil GS (2006) Inflammation and metabolic disorders. Nature 444: 860-867.

52. Saltiel AR, Kahn CR (2001) Insulin signalling and the regulation of glucose and lipid metabolism. Nature 414:799-806.

53. White MF (2002) IRS proteins and the common path to diabetes. Am J Physiol Endocrinol Metab 283: 413-422.

54. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, et al. (1996) IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science 271: 665-668.

55. Taniguchi CM, Emanuelli B, Kahn CR (2006) Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol 7: 85-96.

56. Aguirre V, Uchida T, Yenush L, Davis R, White MF (2000) The c-Jun NH(2)-terminal kinase promotes insulin resistance during association with insulin receptor substrate-1 and phosphorylation of Ser(307). J Biol Chem 275: 9047-9054.

57. Paz K, Hemi R, LeRoith D, Karasik A, Elhanany E, et al. (1997) A molecular basis for insulin resistance. Elevated serine/threonine phosphorylation of IRS-1 and IRS-2 inhibits their binding to the juxtamembrane region of the insulin receptor and impairs their ability to undergo insulin-induced tyrosine phosphorylation. J Biol Chem 272:29911-29918.

58. Kawano K, Hirashima T, Mori S, Saitoh Y, Kurosumi M, et al. (1992) Spontaneous long-term hyperglycemic rat with diabetic complications. Otsuka Long-Evans Tokushima Fatty (OLETF) strain. Diabetes 41:1422-1428.

59. Funakoshi A, Miyasaka K, Shinozaki H, Masuda M, Kawanami T, et al. (1995) An animal model of congenital defect of gene expression of cholecystokinin (CCK)-A receptor. Biochem Biophys Res Commun 210:787-796.

60. Moran TH, Katz LF, Plata-Salaman CR, Schwartz GJ (1998) Disordered food intake and obesity in rats lacking cholecystokinin A receptors. Am J Physiol 274: 618-625.

61. Nakamura M, Yamazaki O, Yamada H, Suzuki M, Horita S, et al. (2011) Stimulatory Effect of Insulin on Renal Proximal Na Transport Is Preserved in Obesity-Induced Insulin Resistant Rats. In: American Society of Nephrology Kidney week 2011. Phiadelphia USA SA-PO2437.

62. Mima A, Ohshiro Y, Kitada M, Matsumoto M, Geraldes P, et al. (2011) Glomerular-specific protein kinase C-β-induced insulin receptor substrate-1 dysfunction and insulin resistance in rat models of diabetes and obesity. Kidney Int 79: 883-896.

63. He Z, Opland DM, Way KJ, Ueki K, Bodyak N, et al. (2006) Regulation of vascular endothelial growth factor expression and vascularization in the myocardium by insulin receptor and PI3K/Akt pathways in insulin resistance and ischemia. Arterioscler Thromb Vasc Biol 26: 787-793.

64. Jiang ZY, Lin YW, Clemont A, Feener EP, Hein KD, et al. (1999) Characterization of selective resistance to insulin signaling in the vasculature of obese Zucker (fa/fa) rats. J Clin Invest 104:447-457.

65. Maric C, Hall JE (2011) Obesity, metabolic syndrome and diabetic nephropathy. Contrib Nephrol 170:28-35.

66. Orchard TJ, Chang YF, Ferrell RE, Petro N, Ellis DE (2002) Nephropathy in type 1 diabetes: a manifestation of insulin resistance and multiple genetic susceptibilities? Further evidence from the Pittsburgh Epidemiology of Diabetes Complication Study. Kidney Int 62: 963-970.

67. Welsh GI, Hale LJ, Eremina V, Jeansson M, Maezawa Y, et al. (2010) Insulin signaling to the glomerular podocyte is critical for normal kidney function. Cell Metab 12: 329-340.

68. Bjørn SF, Bangstad HJ, Hanssen KF, Nyberg G, Walker JD, Viberti GC, Osterby R 1995 Glomerular epithelial foot processes and filtration slits in IDDM patients. Diabetologia 38: 1197-1204.

69. Pagtalunan ME, Miller PL, Jumping-Eagle S, Nelson RG, Myers BD, et al. (1997) Podocyte loss and progressive glomerular injury in type II diabetes. J Clin Invest 99: 342-348.

70. Alsaad KO, Herzenberg AM (2007) Distinguishing diabetic nephropathy from other causes of glomerulosclerosis: an update. J Clin Pathol 60:18-26.

71. Wolf G, Chen S, Ziyadeh FN (2005) From the periphery of the glomerular capillary wall toward the center of disease: podocyte injury comes of age in diabetic nephropathy. Diabetes 54:1626-1634.

72. Park CW, Kim HW, Ko SH, Lim JH, Ryu GR, et al. (2007) Long-term treatment of glucagon-like peptide-1 analog exendin-4 ameliorates diabetic nephropathy through improving metabolic anomalies in db/db mice. J Am Soc Nephrol 18:1227-1238.

73. Isshiki K, Haneda M, Koya D, Maeda S, Sugimoto T, et al. (2000) Thiazolidinedione compounds ameliorate glomerular dysfunction independent of their insulin-sensitizing action in diabetic rats. Diabetes 49: 1022-1032.

74. McCarthy KJ, Routh RE, Shaw W, Walsh K, Welbourne TC, et al. (2000) Troglitazone halts diabetic glomerulosclerosis by blockade of mesangial expansion. Kidney Int 58: 2341-2350.

75. Baylis C, Atzpodien EA, Freshour G, Engels K (2003) Peroxisome proliferator-activated receptor [gamma] agonist provides superior renal protection versus angiotensin-converting enzyme inhibition in a rat model of type 2 diabetes with obesity. J Pharmacol Exp Ther 307: 854-860.

76. Straznicky NE, Grima MT, Lambert EA, Eikelis N, Dawood T, et al. (2011) Exercise augments weight loss induced improvement in renal function in obese metabolic syndrome individuals. J Hypertens 29: 553-564.

This article was originally published in a special issue, **Metabolic Syndrome** handled by Editor(s). Dr. Agathocles Tsatsoulis, University Hospital of Ioannina, USA; Dr. Christa Buechler, University Hospital Regensburg, USA