Ibrahim Card Med J 2023; 13 (1&2): 5-10

EDITORIAL

Type 2 Diabetes: Facts and Fallacies

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Diabetes is one of the leading causes of death and disability worldwide and affects people regardless of country, age, or sex. It is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Type 2 diabetes, which makes up the bulk of diabetes cases, is largely preventable and, in the majority of cases reversible. However, research evidence indicates that diabetes prevalence is increasing worldwide. The gloomy picture is that the prevalence of uncontrolled diabetes is increasing at a galloping pace despite taking antidiabetic medications. A lot of factors might be implicated in the menace. Some of these have already been explicitly described and some have not been described yet or inconspicuously described. The major gap in the management of Type 2 diabetes lies in the mismatch between the evidence gleaned from the research and clinical practice. This highlights the need for a more comprehensive understanding of the disease and innovative strategies to bridge the gap between research evidence and clinical practice. To have a clear concept of the facts and fallacies of type 2 diabetes, let us first have a look at the pathophysiology of type 2 diabetes and the conventional treatment approaches to achieve control over the disease.

Following ingestion of food, foods that contain carbohydrates are converted into glucose. Most of this glucose is sent to bloodstream, causing a rise in blood glucose levels, which prompts the pancreas to produce insulin. The insulin captures the glucose from the blood and take to the target cells (primarily muscle cells, and partly hepatocytes and adipocytes), where they are metabolized to release energy. The leftover glucose is either transformed into glycogen and is temporarily stored in the liver and muscles to be used as fuel in between meals or turned into fat to be deposited in the adipocytes. As the glucose enters the cells, blood glucose levels fall. Four to six hours after eating, this drop reaches a point where the pancreas produces glucagon to offset the effects of insulin. This hormone then signals the liver and muscle cells to convert the stored glycogen back into glucose, by a process known as gluconeogenesis. These cells then release the glucose into the bloodstream so the other cells can use it for energy. This whole feedback loop with insulin and glucagon is constantly in motion to keep the blood sugar levels from dipping too low ensuring a steady supply of energy. With type 2 diabetes, the body makes insulin, but insulin-dependent glucose-utilizing cells do not respond to the action of insulin the way they should. This is known as insulin resistance. Consequently, the cells are not able to take in glucose from the bloodstream leading to a higher blood sugar level. However, the persistent hyperglycemia goes on sending signals to the β-cells of the pancreas to produce an increasing amount of insulin; nonetheless, this extra insulin is unable to surmount the resistance established by the target cells. Over time, some of the β-cells turn fatigued and produce less insulin, which further increases the blood sugar levels. Thus, type 2 diabetes is characterized by both hyperglycemia and hyperinsulinemia (Fig.1).

Faced with this backcloth what could be the aim of an ideal treatment? Before discussing the issue, it

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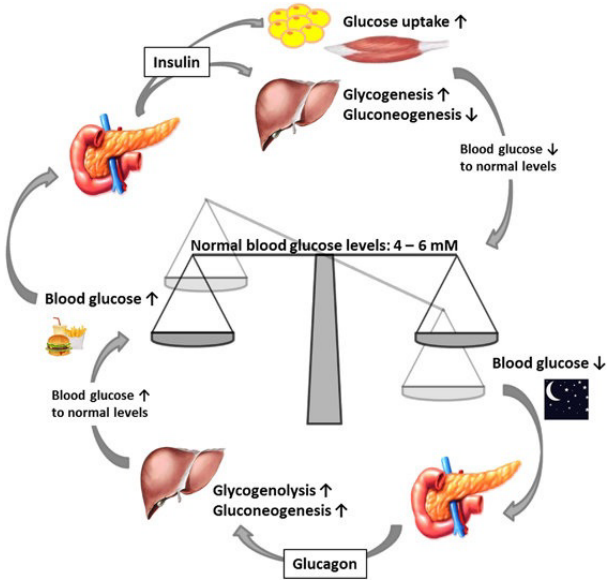

Fig. 1. Maintenance of blood glucose levels by glucagon and insulin (Röder et al[1])

would be worthwhile to discuss what consequences may result from hyperglycemia & hyperinsulinemia if not treated. While constantly high blood sugar levels can cause microvessel diseases leading to blindness, renal failure, amputation, neuropathy, etc. persistently high insulin resistance leads to the development of metabolic syndrome (central obesity, fatty liver disease, hypertension), ischemic heart disease, stroke, dementia, and so on.[2]

The ongoing antidiabetic regimens focus solely on controlling blood sugar to prevent blood sugar-related complications from happening and completely ignore the problem resulting from insulin resistance. Rather treatment makes the second problem (insulin resistance) even worse, particularly if it is done with insulin. Why a type 2 diabetic is treated with insulin when there is enough insulin in the body and the existing insulin has failed to do its job of introducing glucose into the target cells? It is still a myth. So, there is a distinct gap between research data and clinical practice.

Physicians generally equate controlling sugar with diabetes control. But it would not be wise to forget that the presence of sugar in the blood is merely a sign of diabetes, not the disease diabetes itself. Type 2 diabetes is a metabolic disorder and its root cause is insulin resistance. An individual is said to have insulin resistance, when his target cells (muscle cells, hepatocytes and adipocytes), cannot respond well to the action of insulin and fail to receive glucose from the blood for energy. To overcome it, the pancreas tries to make more insulin. For a while, this works and blood sugar levels stay normal. However, over time, the pancreas won't be able to keep up and blood sugar levels rise until prediabetes and frank diabetes develop. The initial treatment of T2DM usually starts with Metformin with the therapeutic goals being to achieve and maintain glycemic targets, mitigate hypoglycemia and reduce the development of complications that lead to morbidity and mortality, especially cardiovascular disease.[3,4] As type 2 diabetes progresses, with loss of β-cell function and increased insulin resistance, the use of agents utilizing pathways dependent on insulin becomes increasingly difficult. The majority of patients fail to achieve their target control of glycosylated haemoglobin (HbA1c) with failure rate being approximately 63%.[3-5] In addition, steady increases in weight are observed in patients with type 2 diabetes.[6,7] Thus, there is still a great unmet need for effective and well-tolerated anti-diabetes agents that can be used in combination with existing treatments to improve glycemic control in patients with type 2 diabetes, in particular without the risk of hypoglycemia and weight gain. Therefore, when metformin fails to achieve glycemic control, add-on combination therapy with two oral anti-diabetes agents is tried.[8] When these combinations also fail, another oral hypoglycemic agent or insulin is added to achieve glycemic control. The addition of insulin helps achieve glycemic control but further aggravates the condition of insulin resistance leading to even more weight gain. As an example, in the study of Henry et al.[9] the mean daily insulin dose required to reduce the HbA1c from 7.7 to 5.1% was 100 ± 24 U/d and was associated with a weight gain of 8.6 kg during a period of 6 months.

This grave situation of type 2 diabetes treatment spontaneously instills some questions in the mind of a medical scientist. Why do the ongoing

antidiabetic regimens fail one after another in bringing control over the disease? Is it enough to introduce glucose into the cells forcibly? Have we ever thought what could be the fate of this glucose if it is not used as energy? Are the cells in a position to make use of this glucose? Probably not. The cells are not metabolically active enough to utilize all the glucose introduced into the cells by an antidiabetic agent, for majority of the diabetic individuals are not accustomed to lead an active life. So, their cells are not metabolically active enough to receive enough glucose to produce energy. That's why they are opposing the action of insulin. In such a situation if glucose is introduced into the cells by boosting the action of existing body insulin with additional insulin from outside sources, what could happen? The excess glucose in the blood (the sign of diabetes) will disappear, but the excess insulin will undoubtedly cause all its ill effects – an increase in obesity, non-alcoholic fatty liver disease (NAFLD), dyslipidemia (high triacylglyerol, low HDL, small dense LDL particles), hypertension, endothelial dysfunction, prothrombotic state, inflammation, ischemic heart disease, stroke, and so on.[10] It is for this reason, that almost all diabetic patients acquire one or more of these complications at one stage of their life, despite some of them maintaining a good glycemic control. The glucose unused by the cells is transformed into fat (triglycerides) with increasing levels of serum triglycerides. Elevated serum triglyceride levels tend to be associated with increased risks of CVD.

Studies conducted both *in vivo* and *in vitro* have shown that insulin, particularly at high concentrations, accelerate the atherosclerotic process through a variety of pathways. These include (i) stimulating de novo lipogenesis, which increases LDL synthesis and secretion[11-13] as a result of SREBP-1C activation and inhibition of acetyl–coenzyme A carboxylase,[14,15] (ii) increased growth and proliferation of vascular smooth muscle cells,[16-23] (iii) activation of genes implicated in inflammation,[24-28] (iv) increased collagen synthesis, [24,29,30] and (v) enhanced transport of LDL cholesterol into arterial smooth muscle cells.[31,32] In line with these *in vitro* actions of insulin, numerous *in vivo* studies have shown that chronic insulin administration in chickens,[33] rabbits,[34] and dogs[35] speeds up the atherogenic process. In addition, a 7–10 day insulin infusion induces hypertension despite maintaining euglycemia;[36] conversely, a brief physiologic hyperinsulinemia in humans results in pronounced salt retention.[37] Finally, it has been noted that insulin therapy in humans is linked to weight gain,[9,38] frequently in conjunction with the development of hypertension and atherogenic dyslipidemia.[39] Inflammation brought on by fat deposits in the artery wall,[28,40,41] directly encourages atherogenesis [42-45] and results in endothelial dysfunction[46], which is linked to accelerated atherosclerosis and insulin resistance.[47,48] The ORIGIN study[49] frequently used as evidence that atherosclerosis is not facilitated by insulin. However, the mean insulin replacement dose in the ORIGIN study was ~34 U/d, which is fairly comparable to the daily secretory quantity of insulin in subjects with normal glucose tolerance (NGT).[50] In contrast, many T2DM patients need >100 U/d to get their HbA1c back to normal (< 6.5 - 7.0%),[9,51-53] and the resulting elevated insulin levels have the potential to trigger the many inflammatory and atherogenic pathways mentioned previously. A body of research data has demonstrated that insulin resistance is a defining trait of nonalcoholic fatty liver disease (NAFLD), even in lean subjects with the disease.[54–56] Moreover, nonalcoholic steatohepatitis (NASH) individuals have a higher risk of cardiovascular disease (CVD).[57,58] Apart from insulin resistance, persons diagnosed with non-alcoholic steatohepatitis (NASH) exhibit several other cardiovascular risk factors, such as inflammation and dyslipidemia.

Thus, the facts generated from the above discussion about type 2 diabetes and fallacies evident in its treatment seem to be in complete mismatch. The present treatment seems to be causing more harm to the patients than to do good. The treatment intends to controlling blood sugar (the manifestation of the disease), rather than to alleviate the root cause of the disease (insulin resistance). In fact, the so-called

treatment makes insulin resistance even worse with appearance of all its side-effects. So, it would not be exaggerated if we say, the present treatment of type 2 diabetes is pushing the patients towards early death and disability. Then what is the way out? Of course, there is a way out. Wait for the next editorial and think of what could be the solution.

REFERENCES

1. Röder PV, Wu B, Liu Y, Han W. Pancreatic regulation of glucose homeostasis. *Exp Mol Med* 2016;48(3): e219. doi: 10.1038/emm.2016.6.
2. Ekberg S. WARNING! Diabetes Treatment Could Actually Kill You!. Dr. Sten Ekberg Reversing Insulin Resistance Naturally [Video]. Uploaded Oct 8, 2021. Available at: https://youtu.be/T7r50X4p6ZY?si=qXxQKu_-0Ody1R-S [Accessed April 6, 2024].
3. Fala L. Tanzeum (Albiglutide): A once-weekly GLP-1 receptor agonist subcutaneous injection approved for the treatment of patients with type 2 diabetes. *Am Health Drug Benefits* 2015;8:126–130.
4. Nyenwe EA, Jerkins TW, Umpierrez GE, Kitabchi AE. Management of type 2 diabetes: Evolving strategies for the treatment of patients with type 2 diabetes. *Metabolism* 2011;60:1–23. doi: 10.1016/j.metabol.2010.09.010.
5. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: A review of current trends. *Oman Med J* 2012;27:269–273. doi: 10.5001/omj.2012.68.
6. Campbell RK. Fate of the beta-cell in the pathophysiology of type 2 diabetes. *J Am Pharm Assoc* 2009;49:S10–5.
7. Morgan CL, Jenkins-Jones S, Evans M, Barnett AH, Poole CD, Currie CJ. Weight change in people with type 2 diabetes: secular trends and the impact of alternative antihyperglycaemic drugs. *Diab Obes Metab*, 2012; 14:424–32.
8. DeFronzo RA, Lewin A, Patel S, Liu D, Kaste R, Woerle HJ et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. *Diab Care* 2015; 38(3):384-93.
9. Henry RR, Gumbiner B, Ditzler T, Wallace P, Lyon R, Glauber HS. Intensive conventional insulin therapy for type II diabetes. Metabolic effects during a 6-mo outpatient trial. *Diabetes Care* 1993;16(1):21–31.
10. Di Pino A, DeFronzo RA. Insulin Resistance and Atherosclerosis: Implications for Insulin-Sensitizing Agents. *Endocrine Reviews* 2019;40(6):1447-67. doi: 10.1210/er.2018-00141
11. Koopmans SJ, Kushwaha RS, DeFronzo RA. Chronic physiologic hyperinsulinemia impairs suppression of plasma free fatty acids and increases de novo lipogenesis but does not cause dyslipidemia in conscious normal rats. *Metabolism* 1999;48(3): 330–337.
12. Winhofer Y, Krss´ak M, Jankovic D, Anderwald CH, Reiter G, Hofer A, Trattnig S, Luger A, Krebs M. Short-term hyperinsulinemia and hyperglycemia increase myocardial lipid content in normal subjects. *Diabetes* 2012;61(5):1210–1216.
13. Scherer T, Lindtner C, O'Hare J, Hackl M, Zielinski E, Freudenthaler A, Baumgartner-Parzer S, T¨odter K, Heeren J, Kr˘s˘s´ak M, Scheja L, F¨urnsinn C, Buettner C. Insulin regulates hepatic triglyceride secretion and lipid content via signaling in the brain. *Diabetes* 2016;65(6):1511–1520.
14. Azzout-Marniche D, B´ecard D, Guichard C, Foretz M, Ferr´e P, Foufelle F. Insulin effects on sterol regulatory-element-binding protein-1c (SREBP-1c) transcriptional activity in rat hepatocytes. *Biochem J* 2000;350(Pt 2):389–393.
15. Lucero D, Miksztowicz V, Macri V, L´opez GH, Friedman S, Berg G, Zago V, Schreier L. Overproduction of altered VLDL in an insulin-resistance rat model: influence of SREBP-1c and PPAR-a. *Clin Investig Arterioscler* 2015; 27(4):167–174.
16. Cusi K, Maezono K, Osman A, Pendergrass M, Patti ME, Pratipanawatr T, DeFronzo RA, Kahn CR, Mandarino LJ. Insulin resistance differentially affects the PI 3-kinase- and MAP kinase-mediated signaling in human muscle. *J Clin Invest* 2000;105(3):311–320.
17. Sasaoka T, Rose DW, Jhun BH, Saltiel AR, Draznin B, Olefsky JM. Evidence for a functional role of Shc proteins in mitogenic signaling induced by insulin, insulin-like growth factor-1, and epidermal growth factor. *J Biol Chem* 1994;269(18):13689–13694.
18. Hsueh WA, Law RE. Insulin signaling in the arterial wall. *Am J Cardiol* 1999;84(1A):21J–24J.
19. Wang CC, Goalstone ML, Draznin B. Molecular mechanisms of insulin resistance that impact cardiovascular biology. *Diabetes* 2004;53(11):2735–2740.
20. Pfeifle B, Ditschuneit H. Effect of insulin on growth of cultured human arterial smooth muscle cells. *Diabetologia* 1981;20(2):155–158.
21. Leitner JW, Kline T, Carel K, Goalstone M, Draznin B. Hyperinsulinemia potentiates activation of p21Ras by growth factors. *Endocrinology* 1997;138(5):2211– 2214.

22. Nakao J, Ito H, Kanayasu T, Murota S. Stimulatory effect of insulin on aortic smooth muscle cell migration induced by 12-L-hydroxy-5,8,10,14-eicosatetraenoic acid and its modulation by elevated extracellular glucose levels. *Diabetes* 1985;34(2):185–191.

23. Golovchenko I, Goalstone ML, Watson P, Brownlee M, Draznin B. Hyperinsulinemia enhances transcriptional activity of nuclear factor-kB induced by angiotensin II, hyperglycemia, and advanced glycosylation end products in vascular smooth muscle cells. *Circ Res* 2000;87(9):746–752.

24. Coletta DK, Balas B, Chavez AO, Baig M, Abdul-Ghani M, Kashyap SR, Folli F, Tripathy D, Mandarino LJ, Cornell JE, Defronzo RA, Jenkinson CP. Effect of acute physiological hyperinsulinemia on gene expression in human skeletal muscle in vivo. *Am J Physiol Endocrinol Metab* 2008;294(5):E910–E917.

25. Golovchenko I, Goalstone ML, Watson P, Brownlee M, Draznin B. Hyperinsulinemia enhances transcriptional activity of nuclear factor-kB induced by angiotensin II, hyperglycemia, and advanced glycosylation end products in vascular smooth muscle cells. *Circ Res* 2000;87(9):746–752.

26. Hajra L, Evans AI, Chen M, Hyduk SJ, Collins T, Cybulsky MI. The NF-kB signal transduction pathway in aortic endothelial cells is primed for activation in regions predisposed to atherosclerotic lesion formation. *Proc Natl Acad Sci USA* 2000;97(16):9052–9057.

27. Hsueh WA. Insulin signals in the arterial wall. *J Cardiol* 1999;84(1):21–24.

28. Reyna SM, Ghosh S, Tantiwong P, Meka CS, Eagan P, Jenkinson CP, Cersosimo E, Defronzo RA, Coletta DK, Sriwijitkamol A, Musi N. Elevated Toll-like receptor 4 expression and signaling in muscle from insulin-resistant subjects. *Diabetes* 2008;57(10): 2595–2602.

29. King GL, Goodman AD, Buzney S, Moses A, Kahn CR. Receptors and growth-promoting effects of insulin and insulinlike growth factors on cells from bovine retinal capillaries and aorta. *J Clin Invest* 1985;75(3):1028– 1036.

30. Lindsey JB, House JA, Kennedy KF, Marso SP. Diabetes duration is associated with increased thincap fibroatheroma detected by intravascular ultrasound with virtual histology. *Circ Cardiovasc Interv* 2009; 2(6):543–548.

31. Stout RW. The effect of insulin on the incorporation of sodium (1-14C)-acetate into the lipids of the rat aorta. *Diabetologia* 1971;7(5):367–372.

32. Porter KE, Riches K. The vascular smooth muscle cell: a therapeutic target in type 2 diabetes? *Clin Sci (Lond)* 2013;125(4):167–182.

33. Stamler J, Pick R, Katz LN. Effect of insulin in the induction and regression of atherosclerosis in the chick. *Circ Res* 1960;8(3):572–576.

34. Duff GL, McMillan GC. The effect of alloxan diabetes on experimental cholesterol atherosclerosis in the rabbit. *J Exp Med* 1949;89(6):611–630.

35. Cruz AB Jr, Amatuzio DS, Grande F, Hay LJ. Effect of intra-arterial insulin on tissue cholesterol and fatty acids in alloxan-diabetic dogs. *Circ Res* 1961;9(1): 39–43.

36. Meehan WP, Buchanan TA, Hsueh W. Chronic insulin administration elevates blood pressure in rats. *Hypertension* 1994;23(6 Pt 2):1012–1017.

37. DeFronzo RA, Goldberg M, Agus ZS. The effects of glucose and insulin on renal electrolyte transport. *J Clin Invest* 1976;58(1):83–90.

38. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, Levy JC. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 2007;357(17):1716–1730.

39. Purnell JQ, Dev RK, Steffes MW, Cleary PA, Palmer JP, Hirsch IB, Hokanson JE, Brunzell JD. Relationship of family history of type 2 diabetes, hypoglycemia, and autoantibodies to weight gain and lipids with intensive and conventional therapy in the Diabetes Control and Complications Trial. *Diabetes* 2003;52(10):2623–2629.

40. Sinha S, Perdomo G, Brown NF, O'Doherty RM. Fatty acid-induced insulin resistance in L6 myotubes is prevented by inhibition of activation and nuclear localization of nuclear factor kB. *J Biol Chem* 2004;279(40):41294–41301.

41. Bhatt BA, Dube JJ, Dedousis N, Reider JA, O'Doherty RM. Diet-induced obesity and acute hyperlipidemia reduce IkBa levels in rat skeletal muscle in a fibertype dependent manner. *Am J Physiol Regul Integr Comp Physiol* 2006;290(1):R233–R240.

42. Wang L, Gill R, Pedersen TL, Higgins LJ, Newman JW, Rutledge JC. Triglyceride-rich lipoprotein lipolysis releases neutral and oxidized FFAs that induce endothelial cell inflammation. *J Lipid Res* 2009;50 (2):204–213.

43. Felton CV, Crook D, Davies MJ, Oliver MF. Relation of plaque lipid composition and morphology to the stability of human aortic plaques. *Arterioscler Thromb Vasc Biol* 1997;17(7):1337–1345.

44. Felton CV, Crook D, Davies MJ, Oliver MF. Dietary polyunsaturated fatty acids and composition of human aortic plaques. *Lancet* 1994;344(8931):1195–1196.

45. Stachowska E, Dołegowska B, Chlubek D, Wesołowska T, Ciechanowski K, Gutowski P, Szumiłowicz H, Turowski R. Dietary trans fatty acids and composition of human atheromatous plaques. *Eur J Nutr* 2004;43(5): 313–318.

46. Steinberg HO, Tarshoby M, Monestel R, Hook G, Cronin J, Johnson A, Bayazeed B, Baron AD. Elevated circulating free fatty acid levels impair endothelium dependent vasodilation. *J Clin Invest* 1997;100(5): 1230–1239.

47. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993;362(6423): 801–809.

48. Cersosimo E, DeFronzo RA. Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. *Diabetes Metab Res Rev* 2006;22(6): 423–436.

49. Gerstein HC, Bosch J, Dagenais GR, D´ıaz R, Jung H, Maggioni AP, Pogue J, Probstfield J, Ramachandran A, Riddle MC, Ryd´en LE, Yusuf S; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367 (4):319–328.

50. Eaton RP, Allen RC, Schade DS, Standefer JC. "Normal" insulin secretion: the goal of artificial insulin delivery systems? *Diabetes Care* 1980;3(2):270–273.

51. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail- Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358(24):2545–2559.

52. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358(24):2560–2572.

53. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360(2): 129–139.

54. Sanyal AJ, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, Luketic VA, Shiffman ML, Clore JN. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. *Gastroenterology* 2001;120(5):1183–1192.

55. Yki-J¨arvinen H. Liver fat in the pathogenesis of insulin resistance and type 2 diabetes. *Dig Dis* 2010;28(1): 203–209.

56. Bugianesi E, Gastaldelli A, Vanni E, Gambino R, Cassader M, Baldi S, Ponti V, Pagano G, Ferrannini E, Rizzetto M. Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. *Diabetologia* 2005;48(4):634–642.

57. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010;363(14):1341–1350.

58. Misra VL, Khashab M, Chalasani N. Nonalcoholic fatty liver disease and cardiovascular risk. *Curr Gastroenterol Rep* 2009;11(1):50–55.