



Commentary

Relationship of Circulating Fatty Acid Profile to Metabolic Disorders Associated with Insulin Resistance



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The epidemic of obesity and type 2 diabetes represents the most frequent causes of morbidity and mortality in developed countries. Obesity is associated with an increased risk of developing metabolic syndrome, hypertension, premature coronary heart disease and stroke. The adverse metabolic effects of obesity may in part be mediated by disorders of lipid metabolism. Normal cellular lipid homeostasis is characterized by the balance between processes that generate or deliver fatty acids (FAs) and processes that utilize these molecules. FAs serve as energy substrate and are important structural component of cell membrane or they are precursors of eicosanoids and regulators of gene expression (Shulman, 2000). In obesity, large amounts of FAs are stored in adipocytes from where may be mobilized and excess of circulating FA and triglycerides leads to the increased lipid accumulation in non-adipose tissues where lipid overload is associated with adverse consequences (Lewis et al., 2002). In skeletal muscle ectopic fat storage, in particular the accumulation of lipid metabolism intermediates (diacylglycerol, long-chain fatty acyl CoA) is suspected to play a key role in the genesis of insulin resistance by interfering with insulin signaling, glucose utilization and by inducing inflammatory pathways (Corcoran et al., 2007). In liver, ectopic lipid accumulation (steatosis) occurs when the rate of FA uptake from circulation and de novo FA synthesis is greater than the rate of FA oxidation and export (as triglycerides in very low density lipoproteins). Lipid overload in pancreatic β -cell leads to dysregulated insulin secretion. There is also evidence that excess of FA causes β -cell apoptosis (Prentki et al., 2002; Kazdová et al., 2002).

Recent meta-analysis of clinical studies provides evidence that not all obese subjects are at increased risk for metabolic disorders, diabetes, and cardiovascular disease. Nearly one-third of obese adults are considered metabolically healthy with the absence of any metabolic disorders such as dyslipidemia, hypertension, insulin resistance (Bell et al., 2014)

or reduced inflammatory status (Phillips and Perry, 2013). It remains unclear which factors may play a role in modification of healthy and unhealthy obesity phenotypes.

Therefore, studying the relationship between lipid metabolism and the status of metabolically healthy or unhealthy obese individuals is of considerable interest.

In this issue of EBioMedicine, Ni et al. report the association of circulation FA profile with metabolic status of obese individuals (Ni et al., 2015). The authors performed metabolomics approach to measure spectrum of circulating free fatty acid (FFA) from 452 individuals of normal weight (NW), metabolically health (MHO) and unhealthy obese subjects (MUO), further before and after weight loss intervention. In the cross-sectional study, FFA levels were found significantly higher in overweight/obese subject with type 2 diabetes in comparison with normal weight or healthy obese subjects. In particular, the higher proportion of dihomo-gamma-linolenic acid (DGLA) and palmitoleic acid was metabolic markers associated with unhealthy obese individuals. Interestingly, the same differences were also found up to ten years before the onset of metabolic syndrome. The weight loss intervention in obese subjects through metabolic surgery or very low caloric diet, improved metabolic disorders and decreased levels of unsaturated fatty acids including DGLA and palmitoleic acid. The authors conclude that some unsaturated FA may have potential role in pathogenesis of metabolic disorders associated with metabolic syndrome and may be a marker in predicting the risk of developing diabetes in obese individuals.

It is well known that increased blood FFA levels have a key role in the development of impaired insulin signal pathways, insulin resistance and type 2 diabetes. However, different kinds of FFA have different effects on carbohydrate and lipid metabolism.

The FA profile in circulation reflects dietary FA intake but is also influenced by the endogenous FA metabolism, mainly by the action of desaturase enzymes ($\Delta 5$, $\Delta 6$) which catalyze the conversion of linoleic acid and linolenic acid into long-chain polyunsaturated FAs and stearoyl coenzyme A desaturase (SCD) which are required for the conversion of saturated FAs into monounsaturated FAs. It has been published that increased SCD activity was associated with insulin resistance, fatty liver and the metabolic syndrome and that high delta-5 desaturase (D5D) activity was associated with lower diabetes risk, whereas high delta-6 desaturase (D6D) activity had opposite effects. It has been established that both high content of palmitoleic acid and low D5D activity index have been described before as BMI-independent predictors of insulin resistance and metabolic syndrome (Kröger and Schulze, 2012).

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The FA profile in circulation is also influenced by the mobilization of FA from triglyceride stores in the adipose tissue. Connor et al. reported that the release of FA into plasma correlated positively with unsaturation and negatively with chain length whereas saturated FA and oleic acid were much less released (Connor et al., 1996). Such a difference could affect subsequent utilization and action of individual FA in other tissues.

In conclusion, the observed difference in FA profile of circulating FFA between MHO and MUO, including the possibility of their influence by weight loss intervention, suggests the potential role of individual FA as important marker and targets for therapy of metabolic disorders associated with insulin resistance and type 2 diabetes. A better understanding of healthy and unhealthy metabolic state associated with obesity is necessary to obtain more knowledge about the relationship between FA profiles in other lipid fractions – mainly in phospholipids to metabolic parameters.

Disclosure

The author declared no conflicts of interest relevant to this article.

References

- Bell, J.A., Kivimaki, M., Hamer, M., 2014. Metabolically healthy obesity and risk of incident type 2 diabetes: meta-analysis of prospective cohort studies. *Obes. Rev.* 15, 504–515.
- Connor, W.E., Lin, D.S., Colvis, C., 1996. Different mobilization of fatty acids from adipose tissue. *J. Lipid Res.* 37, 290–298.
- Corcoran, M.P., Lamon-Fava, S., Fielding, R.A., 2007. Skeletal muscle lipid deposition and insulin resistance: effect of dietary fatty acids and exercise. *Am. J. Clin. Nutr.* 85, 662–677.
- Kazdová, L., Divišová, J., Cahová, M., Marková, I., 2002. Aging-induced impairment of insulin secretion is associated with increased islet triglyceride content in non-obese hereditary hypertriglyceridemic rats. *Diabetologia* 45 (Suppl. 2), 228.
- Kröger, J., Schulze, M.B., 2012. Recent insights into the relation of $\Delta 5$ desaturase and $\Delta 6$ desaturase activity to the development of type 2 diabetes. *Curr. Opin. Lipidol.* 23, 4–10.
- Lewis, G.F., Carpentier, A., Adeli, K., Giacca, A., 2002. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr. Rev.* 23, 201–229.
- Ni, Y., et al., 2015. Circulating unsaturated fatty acids delineate the metabolic status of obese individuals. *EBioMedicine* 2, 1513–1522.
- Phillips, C.M., Perry, I.J., 2013. Does inflammation determine metabolic health status in obese and nonobese adults? *J. Clin. Endocrinol. Metab.* 98, 1610–1619.
- Prentki, M., Joly, E., El-Assaad, W., Roduiz, R., 2002. Malonyl-CoA signaling, lipid partitioning, and glucolipotoxicity: role in β -cell adaptation and failure in the etiology of diabetes. *Diabetes* 51, S405–S413.
- Shulman, G.I., 2000. Cellular mechanisms of insulin resistance. *J. Clin. Invest.* 106, 171–176.