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# Comparison of the metabolomic signature of diabetes and the oral glucose tolerance test

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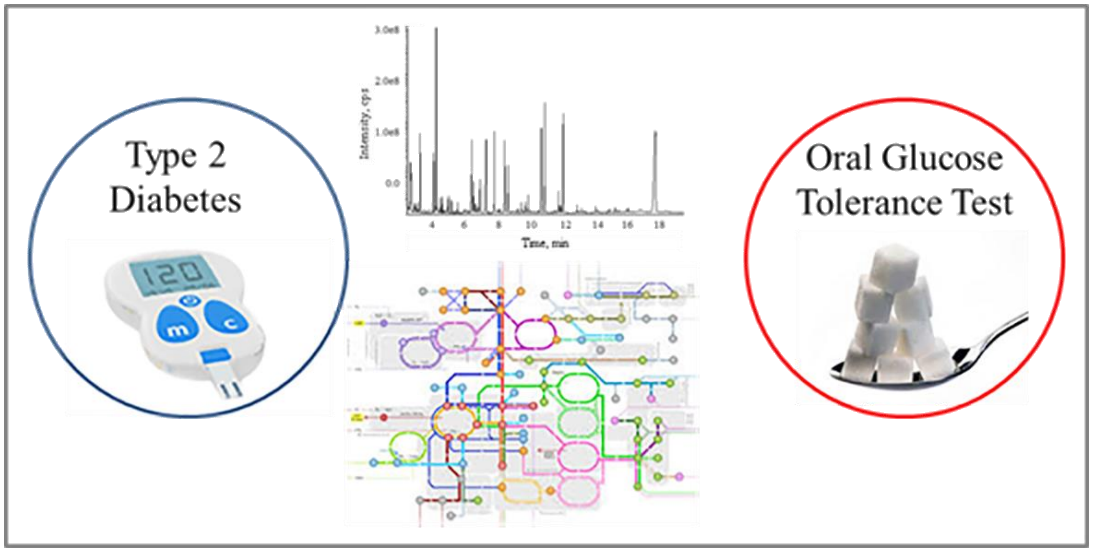
# Comparison of the metabolomic signature of diabetes and the oral glucose tolerance test



**Abstract:**
Intervention trials attempt to clarify the possible effects of certain challenge tests on study subjects (e.g. drugs effectiveness, environmental exposure experiments), while observational studies employ free-living populations to analyze the relationship between a particular effect and possible triggering factors. Based on the hypothesis under investigation, the researcher will choose the appropriate study design. Nevertheless, here we report the utility of combining observational and interventional studies to discover confident biomarkers in the clinical field. We contrasted metabolomic profiles related with diabetes and the oral glucose tolerance test (OGTT), a clinical test used to simulate the hyperinsulinemia observed in diabetes. We found that the main metabolic changes occur in the same metabolite classes, including energy-related metabolites, amino acids (especially brain chain amino acids, BCAA) and multiple lipids, such as free fatty acids, acyl-carnitines, triglycerides and phospholipids, among them. Hence, challenge tests such as the OGTT guarantee to be a great strategy to investigate pathological signatures associated with the development of diseases as a previous step before performing validation works in observational studies.

**Keywords:** metabolomics; diabetes; oral glucose tolerance test

# Introduction

## Observational study design

The study population is not under control, the investigator simply 'observes' and evaluates the relationship between a given outcome and possible triggering or associated factors

large sample sizes are needed to minimize inter-subject variability

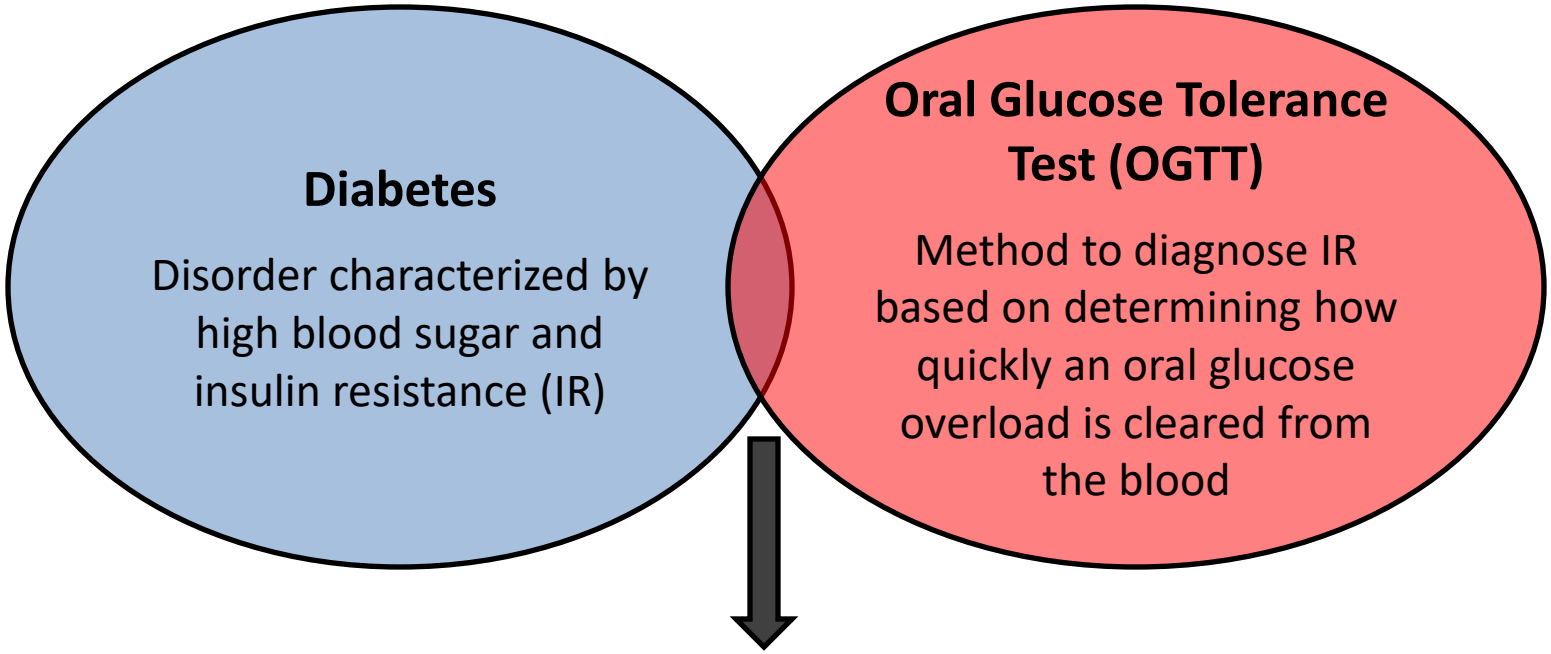
## Intervention study design

Direct assessment of the effect of a particular intervention on the investigated outcome

the controlled environment allows sharpening metabolic alterations, thus simplifying the experimental design

the combination of complementary observational and interventional studies stands out as a very reliable strategy to discover confident metabolomic biomarkers

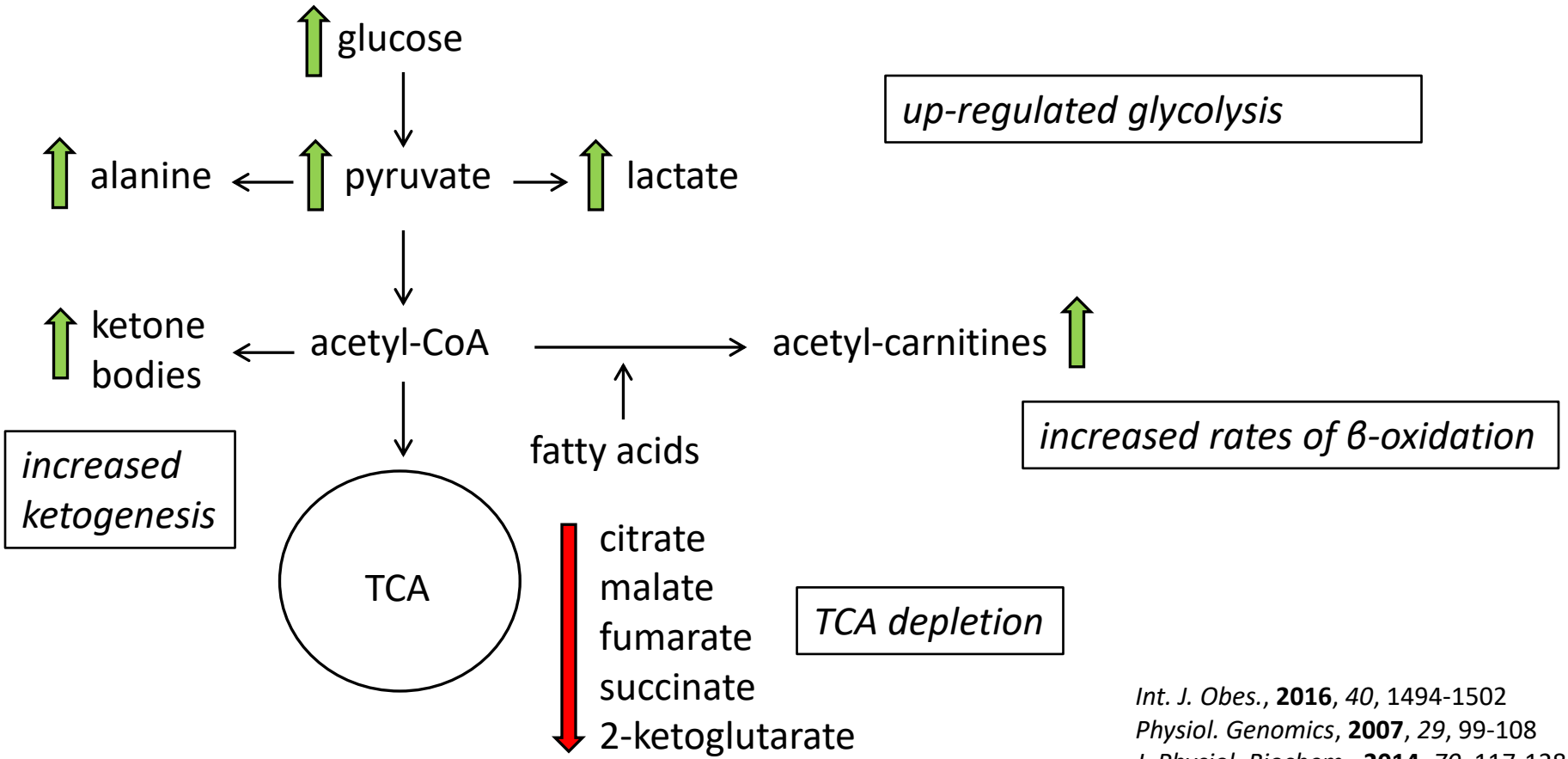
# Introduction




the OGTT can be used to elucidate pathological hallmarks of diabetes and related metabolic disorders, as well as to better understand how different people respond in different ways to the same stimulus, setting the basis for a more personalized medicine

# Results and discussion: Metabolomics in diabetes

## Alterations in energy metabolism





*Int. J. Obes.*, **2016**, *40*, 1494-1502
*Physiol. Genomics*, **2007**, *29*, 99-108
*J. Physiol. Biochem.*, **2014**, *70*, 117-128

# Results and discussion: Metabolomics in diabetes

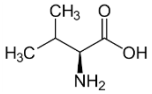
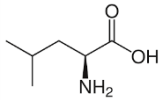
## Homeostasis of amino acids

hyperinsulinemia

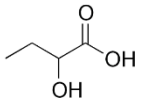
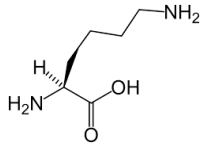
↓

*over-activated proteolysis and gluconeogenesis*

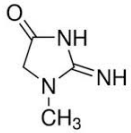
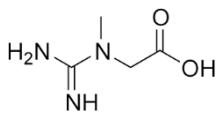
↑ amino acids (branched chain amino acids)

↑ precursor organic acids (3-methyl-2-oxovalerate, 2-hydroxybutyrate, 2-aminoadipate)

↑ protein catabolism metabolites (creatine, creatinine)

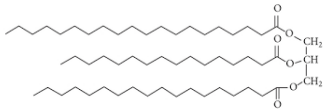
*Chromatographia*, **2009**, *69*, 941-948
*Diabetes*, **2013**, *62*, 4270-4276
*Clin. Chim. Acta*, **2018**, *477*, 39-47

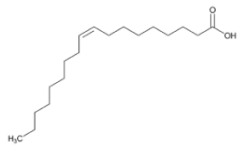
# Results and discussion: Metabolomics in diabetes

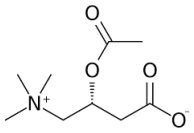
## Lipidomic perturbations

*Accumulation of total lipids*

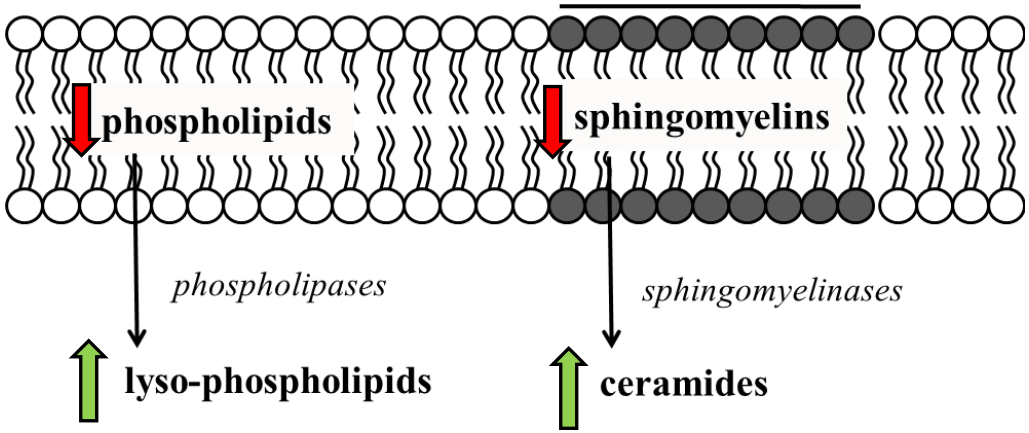
- ↑ triglycerides
- ↑ free fatty acids
- ↑ acyl-carnitines







*Metabolism of membrane lipids*





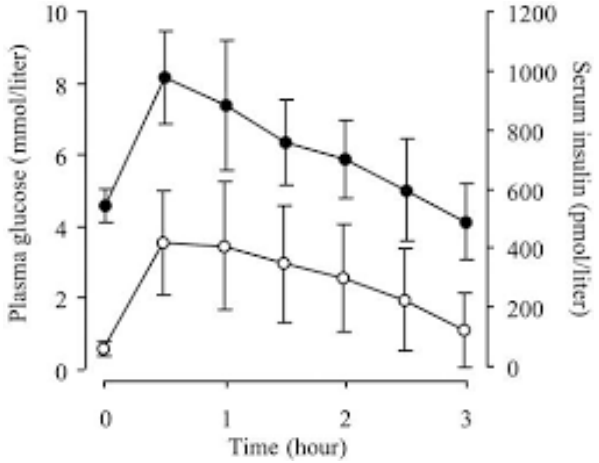
*Diabetologia*, **2016**, *59*, 2349-2359
*J. Proteome Res.*, **2009**, *8*, 1623-1630
*J. Physiol. Biochem.*, **2014**, *70*, 117-128
*J. Exp. Med.*, **2008**, *205*, 2975-2984
*Talanta*, **2011**, *85*, 1711-1720

# Results and discussion: Metabolomics in OGTT

## Alterations in energy metabolism

acute intake of carbohydrates causes a transitory hyperinsulinemic state, which promotes glucose uptake and switches the organism from catabolism to anabolism

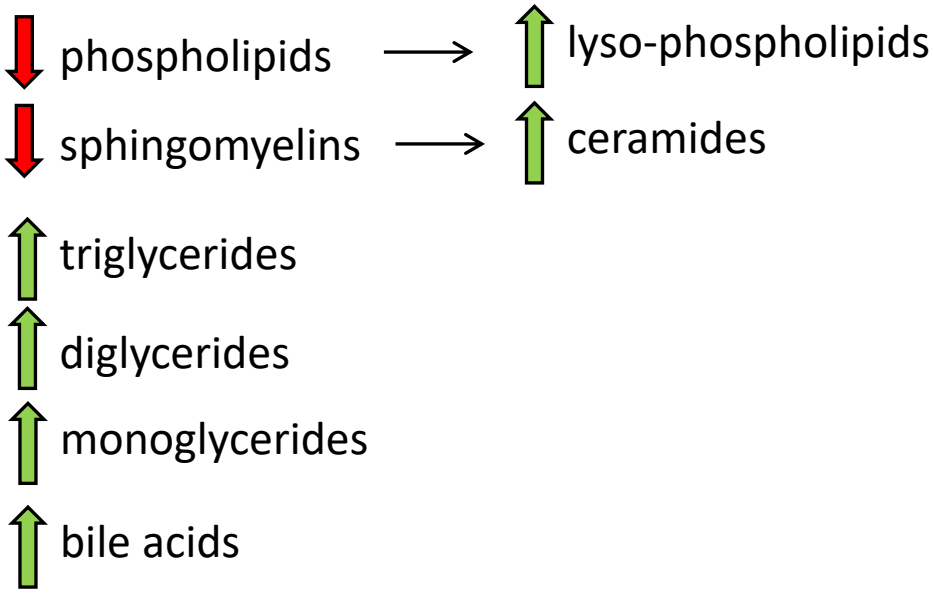
- ↑ glucose metabolism
- ↓ β-oxidation
- ↓ lipolysis
- ↓ ketogenesis
- ↓ proteolysis
- ↓ gluconeogenesis




*Mol. Syst. Biol.*, **2008**, *4*, 1-9
*Electrophoresis*, **2017**, *38,* 2313-2322
*AJP Endocrinol. Metab.*, **2008**, *296*, E384-E393
*Metabolomics*, **2010**, *6*, 56-66

# Results and discussion: Metabolomics in OGTT

**Lipidomic perturbations**




*Electrophoresis*, **2017**, *38,* 2313-2322
*AJP Endocrinol. Metab.*, **2008**, *296*, E384-E393
*Diabetes*, **2013**, *62*, 2689-2698
*Mol. Syst. Biol.*, **2008**, *4*, 1-9

# Conclusions

- Metabolomics has demonstrated that similar metabolic disturbances occur in patients affected by diabetes and subjects undergoing an oral glucose tolerance test (OGTT)

- The most important metabolic alterations have been found in circulating levels of carbohydrates and related energy-metabolites, amino acids and lipids, thus evidencing profound impairments in energy metabolism and dyslipidemia

- Challenge tests provide a great opportunity to investigate pathological hallmarks associated with the development of diseases in a feasible manner s a starting point before to be validated in larger observational studies.