Mashael Al-Jaber et al., J Diabetic Complications Med 2018, Volume 3
DOI: 10.4172/2475-3211-C1-002



## Combined metformin and insulin treatment reverses metabolically impaired omental adipogenesis and accumulation of 4-hydroxynonenal in obese diabetic patients

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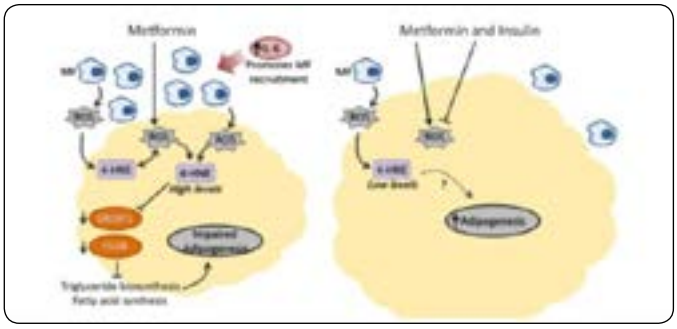
**Objective:** Obesity-associated impaired fat accumulation in the visceral adipose tissue can lead to ectopic fat deposition and increased risk of insulin resistance and type 2 diabetes mellitus (T2DM). This study investigated whether impaired adipogenesis of omental (OM) adipose tissues and elevated 4-hydroxynonenal (4-HNE) accumulation contribute to this process, and if combined metformin and insulin treatment in T2DM patients could rescue this phenotype.

**Methods:** OM adipose tissues were obtained from forty clinically well characterized obese individuals during weight reduction surgery. Levels of 4-HNE protein adducts, adipocyte size and number of macrophages were determined within these tissues by immunohistochemistry. Adipogenic capacity and gene expression profiles were assessed in preadipocytes derived from these tissues in relation to insulin resistance and in response to 4-HNE, metformin or combined metformin and insulin treatment.

**Results:** Preadipocytes isolated from insulin resistant (IR) and T2DM individuals exhibited lower adipogenesis, marked by upregulation of anti-adipogenic genes, compared to preadipocytes derived from insulin sensitive (IS) individuals. Impaired adipogenesis was also associated with increased 4-HNE levels, smaller adipocytes and greater macrophage presence in the adipose tissues. Within the T2DM group, preadipocytes from combined metformin and insulin treated subset showed better *in vitro* adipogenesis compared to metformin alone, which was associated with less presence of macrophages and 4-HNE in the adipose tissues. Treatment of preadipocytes *in vitro* with 4-HNE reduced their adipogenesis and increased proliferation, even in the presence of metformin, which was partially rescued by the presence of insulin.

**Conclusion:** This study reveals involvement of 4-HNE in the impaired OM adipogenesis-associated with insulin resistance and T2DM and provides a proof of concept that this impairment can be reversed by the synergistic action of insulin and metformin. Further studies are needed to evaluate involvement of 4-HNE in metabolically impaired abdominal adipogenesis and to confirm benefits of combined metformin-insulin therapy in T2DM patients.




The effect of 4-HNE, metformin and insulin treatment on ROS production and OM adipogenesis.

### Recent Publications

1. A book: Al-Jaber M, Mohamed-Ali V. (2016). Frayn, K. N., Stanner, S., Foundation, B. N. (Eds.). In Cardiovascular Disease: Diet, Nutrition and Emerging Risk Factors. 2nd edition, Wiley-Blackwell. Submitted.
2. Non-acute responses of hematological and molecular markers to intermittent hypoxic exposure and physical exercise in hot environment. DOI: 10.5339/qfarf.2012.BMP60.
3. Role(s) of microRNAs as markers and mediators of insulin resistance. DOI: 10.5339/qfarf.2013.BIOP-040.

4. Combined metformin and insulin treatment reverses metabolically impaired omental adipogenesis and accumulation of 4-hydroxynonenal in obese diabetic patients. DOI: 10.1016/j.redox.2017.03.012. Epub 2017 Mar 16.
5. Comparison of Cardiometabolic Risk Factors in Metabolically Healthy and Pathologically Obese Arabs and Caucasians. Qatar Foundation Annual Research Conference Proceedings, HBPP2662.

**Biography**

Mashael Aljaber the head of Molecular Biology, where she worked on the effect of diabetes in the biological pathways for the RNA transcriptome and proteins from the blood and skeletal muscles. Evaluating the effect of obesity and its effects for diabetes (diabesity). In addition to the environmental effect for the diabesity.

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**Notes:**