Insulin Hormone Role in the Organizing of Mitochondrial Functions: A review

Noora M. Hameed1, Hadeel Alaa Al-Rubaie2, Hawaa Sabah Al-Musawi3, Mona N. Al-Terehi4

1Al-Nisour university college- Anesthesia technique/Iraq
2University of Babylon- DNA research center/Iraq
3University of Babylon, College of Science for Women/Iraq
4Babylon university- College of sciences/Iraq

Corresponding Author: Noora.anesth@nuc.edu.iq

ABSTRACT
Insulin is one of the important hormones in human body, it contributed in different cellular processes included mitochondria, in present review the role of insulin organizing of mitochondrial biogenesis, degradation, and function was discussed, the impact of insulin impairment in type 1 and insulin resistance in type 2 have mischievous influences on mitochondrial role, foremost in skeletal muscle and in several organs like liver heart, kidneys, and the brain. Deficient in secretion of insulin level and action may elucidate many of the variations in mitochondrial functions that noticed in diabetes types, and in fact demonstrate how the changes in mitochondrial function can participate to variety pathologies in diabetes. From this can be concluded that there were linked between insulin and mitochondria at different cellular functions.

INTRODUCTION
The mitochondria are cellular compartments that generate the plurality of a cell's Adenine triphosphate (ATP) from nutrients using two pathways; the oxidative phosphorylation (OXPHOS) and the cellular respiration, The Mitochondria’s major functions in addition to cellular respiration, is in fact linked with variety of assignments like β-oxidation, removal toxic materials and diversion of acetyl-CoA that formation in the fatty acids (FAs), glucose molecules, AA oxidation during the cycle of tricarboxylic acid (TCA); the chain of mitochondrial electron transport (ETC) complicated actions, and finally generation of reactive oxygen species (ROS) (1, 2).

Mitochondria having nearly about 1000- 1,500 preponderantly proteins which genomic DNA encoded in addition to 13 proteins found in mitochondrial DNA, about 37 genes, included 22 genes encoded to tRNA and two subunits of RNA in human, and all are crucial to preserve the mitochondrial role (3). The mitochondrial process like replication, biogenesis including the transcription, translation, balance of proteomic, and the role of mitochondria is tightly organized and extremely intricate.

As roughly all cellular operations demand the presence of ATP, it is expected that the pathological and physiological variations in energy requirements and fuel alimentation effects the roles of mitochondria, involving the mitochondrial dynamics (incorporation and cleavage), biogenesis, and mitophagy (4).

Variety of mitochondrial labors in insulin-deficient and insulin-resistant states
The occurrence worldwide of diabetes disease, particularly the diabetes mellitus type 2 (T2D), and related international economic concern are fundamental and fast mounting, with counteractive effects on social security and health systems (5). In spite of identified T2D by the resistance of insulin and imperfect secretion of insulin and type 1 diabetes (T1D) diagnosed via ultimate insulin incompetence, both types have different etiologies (6), deeply disrupt fuel metabolism, involving glucose metabolism, fat, and amino acids (AAs), the major fuel provenance to cell processes.

Furthermore, well-authenticated up organization of oxygen exhaustion in T1D and T2D refers the elevation expenditure of resting energy in non-treated patients (7, 8). Emerging evidence clearly refers that the changes in the energy metabolism can be traced to the mitochondria. Insulin considered the predominant hormone in the metabolism of fuel, is contributed in variety of assignments in the cells, include the turnover of proteins, a robustly ATP-dependent operation; Furthermore, insulin deteriorations in diabetes is connected with changed energy metabolism.

The primary goal is to largely highlight the impact of insulin impairment in type 1 and insulin resistance in type 2 have mischievous influences on mitochondrial role, foremost in skeletal muscle and in liver, kidney, adipose tissue, heart and the brain. (9-13).

Insulin hormone role in mitochondrial processes
The signaling of insulin pathway and it connects with receptor (IR) enhancing the IR auto phosphorylation, persuading insulin receptor substrate (IRS) adaptor proteins, and AKT pathway energizing (14). The insulin/IRS/AKT passageway is focal to glucose balance and adjusts diversified ATP-dependent operations involving catalyzing the uptake of glucose in muscles and adipose tissue, suppressing glucose emission and glycogenesis, enhancing lipid storage and production in both adipose tissue and liver, in addition to coordinating protein production and dissolution. The insulin-IRS-AKT passageway's organizations of mammalian target of rapamydin (mTOR) efficacy and FOXO transcription factors which have role inclusions for assignment of mitochondria, as mTOR (15, 16) and FOXO1 (17,18) organize oxidative role of mitochondria through the organization of PPARy co-activator 1α (PGC1A)

PGC1A is a prime governor of the biogenesis of mitochondria through both nuclear respiratory factor 1 (NRF1) and NRF2, that organizes the nuclear and mitochondrial-encoded genes by transcription factor A of mitochondria (TFAM) (19). All mitochondrial proteins
encoded in genomic DNA imported into the mitochondria after produced in ribosomes, while mitochondrial ribosomes produce about 13 mitochondrial proteins (20). The compounds of mitochondria generated from both the imported nuclear and proteins encoded by mitochondrial genome Insulin’s duty in the outer and inner mitochondrial membrane transporters and complexes productions stays vague, Mitochondrial protein production and rotation are crucial for preserving protein in characteristic. Isolated Insulin’s impact on protein production highly differ between various tissues and proteins (24), Stump and others (25) proved that the elevation in physiological level of insulin casting in the normal individuals raised the ATP generation in real time secluded mitochondria from skeletal muscle of human. In similar way, insulin casting elevated mRNA of mitochondrial genes like NADH dehydrogenase subunit IV (MT-ND4) and genomic genes encoding the proteins of mitochondrial such as cytochrome c oxidase subunit IV (COX4) raised mitochondrial protein generation, and raised the effectiveness of the clef metabolic enzymes COX and citrate synthase in muscle. In the normal individuals, the high insulin concentricity trigger production of mitochondrial protein in muscles, but only when co-infused with amino acids (26), as intense insulin pouring out reduces the plasma amino acids concentrations via inhibiting protein degeneration (27, 28). Similar to the mitochondrial protein production, elevation in the enzyme actions of mitochondria and ATP generation also rely on amino acids availability. In adults insulin casting without amino acids complementation intake up regulated the COX3, PGC1α, and NRF1 gene expression though, insulin alone flopped to increased protein production in mitochondria of muscles, COX and CS action, generation of ATP, in addition to phosphorylation of the protein assembly enhancers 4EBP1, p70S6K in addition to mTOR (29). In a similar manner, Liesa et al. (30) linked elevated the PGC1α mRNA with raised oxidation of glucose pursuing insulin casting but noticed that PGC1α protein scale was unchanged in the muscles. These oversights (25, 26, 29, 31) referred to that insulin triggers the transcription of a special genes with prospect impacts on the function of mitochondria, but only induces the expression and mission of mitochondrial proteins when proper amino acids concentrates are existing. Insulin suppresses not only the degeneration of endogenous proteins but fat preserving too. So, when carbohydrates alone are digested, the insulin signaling enhances utilization of carbohydrate for energy demands, maintaining the fat and protein storage. Although of both amino acids and insulin are required for protein production, carbohydrate or fat alone is improbable to enhance protein generation. So, it’s expected that protein digestion is connected with higher thermogenesis than carbohydrate and fat consuming, probable due to synthesis of proteins higher ATP request (32), (34). It stays infirm whether carbohydrate-stimulate raises in the insulin signaling flop to trigger protein production in muscle (particularly in mitochondria) so as to keep amino acids for the assembly of substantial proteins, like the clotting factors in liver, when amino acids availability is restricted. Genetic manipulation studies in mice have applied molecular associations between mitochondrial role and insulin signaling. Investigations found that the removal of IR in the heart muscles and brain reduces the mitochondrial respiration and oxidative stress elevation in addition to inhibit generation of ATP and fatty acid oxidation (FAO) in heart (33–35). The knockout of Adipose-specific IR lowers mitochondrial purport and oxygen exhaustion in brown adipose tissue (BAT), whilst the lowering white adipose tissue (WAT) bloc by upon 90% (36). In a similar manner, synthesis of ATP is lowered in β cell-specific IR-knockout mice in spite of raised oxygen consuming, and retrieving the expression of IR in β cells iterated the defect in mitochondrial ATP synthesis, proposing that the insulin hormone organizes function of mitochondrial β cell (37). The cardio myocyte-specific removal of Irs1 and Irs2 lowered ADP-enhanced consumed of oxygen and ATP generation accompanied with down regulation of FAO and OXPHOS genes in mitochondria (38). Similar lowering found in FAO and morphology of mitochondria in heart followed double knockout (DKO) of IR and IGF1 receptor (Igf1r), that signaling cascades get together at IRS proteins (39). Researches in Irs1/-/DKO mice applied mechanistic associations between hepatic insulin function and mitochondrial role. Plugging hepatic insulin signaling in Irs1/-/DKO mice causes resistance to insulin and FOXO1 hyper activation, which ruptured ETC combinations and minimized NAD+ level (40). As a result, the NAD+-dependent protein deacetylase SIRT1 lowers its de acetylation of PGC1α, reducing mitochondrial biogenesis and drastically inhibiting mitochondrial coupling and ATP generation (17). So, insulin thought of promote the functions of mitochondria by PGC1α redox regulation, studies present that insulin enhances mitochondrial respiration in isolated cortical neurons from healthy mice but not Alzheimer’s disease-prone (AD-prone) apo lipoprotein E e4-knock in mice (41). Given that 80% of AD patients present inhibited glucose tolerance or T2D (42), and the AD brain shows insulin resistance and inhibited mitochondrial function (43, 44), strategies that promote insulin sensitivity in diabetes may also have therapeutic value in AD. Collectively, these data prove importance of insulin for normal mitochondrial function in multiple tissues. Sergi et al (45) suggested that the dysfunction of Mitochondria is linked to the insulin resistance pathogenesis in the T2D, but this relation still under investigations whilst some evidences suggests that enhancing the function of mitochondria may elucidate a valuable therapeutic tool for insulin sensitivity enhancing. Also they exhibited the mechanistic pathway of insulin resistance with mitochondrial dysfunction in skeletal muscle alongside the intracellular pathways orchestrating mitochondrial bioenergetics.

REFERENCES


