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Smoking and Glucose Homeostasis

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Smoking is usually associated with vascular complications, especially with ischaemic disease of the lower limbs and with ischaemic heart disease, but pulmonary cancer represents another serious consequence of smoking. Smoking cessation brings a great problem to many patients even though they are treated for the aforementioned complications. Diabetes mellitus is frequently accompanied by vascular changes because an increased glucose concentration accelerates oxidative stress and other pathogenic mechanisms leading to microvascular and macrovascular diseases. However, vascular changes in diabetes represent one area in which deleterious effects of smoking are present. Besides this, smoking is related to the regulation of glucose metabolism.

Epidemiological remarks

Smoking is a risk factor in the diabetes development as it was documented by epidemiological data. Meta-analysis of 25 prospective studies involving more than 1.2 million persons demonstrated an increased number of people with diabetes among smokers. The relative risk was step-wise increased from former smokers (RR = 1.23) and "mild" smokers (RR = 1.29) to "heavy" smokers (RR = 1.61) compared to never-smokers [Willi 2007]. This observation confirms that smoking could play a certain role in the development of impaired glucose homeostasis in man.

Other data show the relationship of smoking and mortality in people with type 2 diabetes. A total of 7401 women was evaluated according to the number of cigarettes used and an increased mortality was found in women proportionally to the number of cigarettes [Al Delaimy 2001]. In heavy smokers (> 35 cigarettes/day) without diabetes the mortality was nearly tripled whereas it was doubled in smokers compared to non-smokers with diabetes. The higher mortality was due to both cardiovascular and oncological diseases in smokers.

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Smoking and insulin secretion

The relationship of smoking to insulin secretion is much less understood than the effect on the vascular system. However, the nicotine exposure has significant impact in all persons without or with diabetes. The nicotine receptors were described on pancreatic beta cells already 15 years ago [Yoshikawa 2005]. Experimental studies with rat and human islets of Langerhans incubated in medium with different concentrations of nicotine demonstrated a decreased insulin secretion stimulated by glucose. This reduction was dependent on nicotine concentration used in both islets from rats and men but it was more pronounced when 27,0 mmol/l glucose was added to the medium. This study confirmed the inhibitory effect of nicotine on insulin secretion. A recent study documented a decreased insulin secretion into medium "in vitro" [Hui 2018]. A decreased insulin content in the incubated beta cells and their accelerated apoptosis were observed as well. The alternative pathway involving mitogen-activated protein kinase (p38MAPK) elucidates the mechanism by which cigarette smoking extract impairs beta cells.

In addition, clinical data may confirm a negative effect of cigarette smoking on insulin secretion. The Japanese "The Saku Study" evaluated the quantitative effect of cigarette smoking on insulin secretion in 1199 men without diabetes [Morimoto 2013]. More cigarettes consumed were associated with lower insulin secretion. A worsening of insulin secretion was apparent in smoking women and smoking men compared with non-smokers in another study [Oba 2015]. More frequent manifestation of diabetes and prediabetes was observed in smoking men whereas passive smoking in women had such an effect as well. This study demonstrated the relationship between impaired insulin secretion in smokers and possible development of diabetes.

Smoking and insulin sensitivity

The effect of smoking on insulin sensitivity is another feature besides the deleterious effect on insulin secretion. A strongly decreased insulin action was found in heavy smokers compared to non-smokers [Hui 2018]. The exposition to tobacco smoke in one experimen-

tal study caused decreased plasma adiponectin concentrations together with its enhanced accumulation in adipocytes [Li 2015]. These results may indicate that hypoadiponectinaemia induced by tobacco smoking may be associated with impaired insulin action and with increased risk of diabetes development in smokers [Li 2015].

Nicotine was found as a substance causing insulin resistance. It significantly impairs the insulin signaling status by increasing oxidative stress which inhibits the downstream phosphatidylinositol-3-kinase (PI3K) and Nrf2 phosphorylation. This nuclear factor erythroid 2-related factor 2 (Nrf2) has a pivotal role in nicotine-induced insulin resistance as confirmed recently in an experimental study on cardiomyocytes in mice [Li 2019]. The administration of antioxidants could improve the insulin-stimulated glucose uptake in nicotine-treated mice. Thus, accelerated oxidative stress has a main role in deterioration of insulin-signaling cascade and insulin resistence development in smokers.

Smoking and development of type 2 diabetes

The relationship between smoking and development of type 2 diabetes is based both on experimental and clinical observations. Important results were obtained in an experimental study with prenatal nicotin exposition which caused a diminished endocrine pancreatic islet size [Somm 2008]. Their number was reduced in the postnatal seventh day in offsprings. Significantly decreased gene expression of transcription factors Pax-6 and Nkx6.1, and of hormones such as insulin and glucagon together with hypertrophy of adipose tissue in later development were further characteristics observed in these offsprings. These findings confirm a severe deterioration of endocrine pancreas and dysregulation of adipose tissue originating in the early fetal development of nicotine-exposed rats.

Smoking in people with type 2 diabetes demonstrates not only a decreased insulin secretion from the beta cells but also molecular mechanism of this dysfunction [Hui 2018]. The administration of p38MAPK inhibitor prevented the enhanced apoptosis and dysfunction of beta cells induced by cigarette smoking extract. This study confirms that smoking activates p38MAPK which is involved in beta-cell apoptosis and thus it contributes to the type 2 diabetes development in smokers.

Nicotine accelerates oxidative stress in the beta cells. Its exposition to female rats during pregnancy significantly increased reactive oxygen species and protein carbonyls which caused mitochondrial damage and dysfunction of the beta cells in offspring [Jennifer 2008]. Structural mitochondria defects observed in the three-week old animals worsened with age and were followed by glucose intolerance which was caused by impaired insulin secretion. This experimental study confirms direct effects of nicotine on structural and functional changes of the beta cells in offspring of mothers exposed to nicotine during gestation.

Beta cells have in their cell membrane nicotine-acetylcholine receptors activated by nicotine inducing increased oxidative stress and mitochondrial damage. Activated caspases then initiate the beta-cell apoptosis. The intracellular changes are the same as in people with type 2 diabetes. Folic acid and vitamin B_{12} protect from deleterious nicotine effect on mitochondria [Bhattacharjee 2018]. Nicotine inhibits the activities of scavenger enzymes such as superoxide dismutase, catalase and glutathione reductase whereas the preincubation with folic acid and vitamin B_{12} prevents this inhibitory effect.

In conclusion, the negative effect of nicotine on mitochondria and beta-cell function may explain more frequent development of type 2 diabetes in smokers compared to non-smokers. The molecular mechanisms are the same as in typical type 2 diabetes and accelerated oxidative stress is the main causative factor responsible for the mitochondria failure and beta-cell death.

Smoking and vascular disease in diabetes

Negative effects of smoking on the vessel wall have been repeatedly confirmed in a number of studies. In diabetes, the effect of smoking is combined with the influence of diabetes itself on the vascular system although several other factors have been described. Plasma triglycerides increase the risk of vessel wall impairment (1,73-fold) in type 2 diabetes whereas the risk was still higher in smokers (3,06-fold) [Valdivielso 2007].

The effect of smoking on microangiopathy development is demonstrated by a significantly increased number of complications in smokers compared to non-smokers. This is due to decreased oxygen tension found by transcutaneous oxygen measurement [Huang 2017]. A total of 436 people with type 2 diabetes were enrolled in this study and the risk of microangiopathy development was ten times higher in patients with low oxygen tension than in those with normal tension. Smoking as a risk factor increased the occurence of microangiopathy by 2,76-fold.

Smoking is directly related to endothelial dysfunction [Abdelghany 2018]. It causes dysfunction of nitric oxide synthase in the endothelium followed by decreased nitric oxide and increased superoxide production. Smoking decreases the production of tetrahydrobiopterin which is essential for the function of nitric oxide synthase. The addition of tetrahydrobiopterin or superoxide dismutase definitely improves the endothelium status. Cigarette smoking increases oxidative stress and thus creates reactions causing endothelial dysfunction. The same principle is present in the diabetic foot syndrome and smoking cessation has therefore fundamental effects on further improvement in ulcer healing [Xia 2019]. All medical arrangements lowering oxidative stress may suppress development of endothelial dysfunction.

Smoking increases the risk of thrombosis. An experimental study with endothelial cells from umbilical cord (HUVEC) demonstrated that the cigarette smoking extract causes a decreased gene expression of thrombomodulin localized on the surface of endothelial cells [Wei 2019]. Thrombomodulin inhibits thrombin by activated protein C which has an anticoagulatory effect. Such an effect arises after six hours of the endothelial cell exposi-

tion with cigarette smoke. This study demonstrates a molecular mechanism by which cigarette smoke induces increased thrombotic risk.

Our present knowledge supports the evidence of the complex mechanism both in the vascular wall and in the circulating blood by which smoking impairs the vascular system.

Smoking cessation, vaping and glucose regulation

Smoking cessation is a serious problem especially in people with diabetes who have faster nicotine metabolism and tend to have a higher consumption of cigarettes [Keith 2019]. Partial agonists of nicotine-acetylcholine receptors on beta cells (vareniclin) or antagonists of these receptors (bupropione) were tested [Woynillowicz 2012]. However, all these substances inhibit the glucose-stimulated insulin secretion. An impaired respiratory chain was found in mitochondria of beta cells.

Vaping (e-cigarettes) brings less nicotine to the organism but it significantly decreases brain glucose utilization in ischaemic stroke [Sifat 2018]. Impaired GLUT1 expression was found as a consequence of deleterious nicotine action. Nicotine or e-cigarette vaping could create a significantly glucose-deprived state at the ischaemic brain which may lead to worsened stroke outcome and recovery [Sifat 2018]. Positive effects of metformin and rosiglitazone partly counterbalancing the ischaemic brain injury due to nicotine exposure were recently reported [Kaisar 2017, Sivandzade 2019]. In summary, e-cigarettes do not bring any advantage compared to classical tobacco smoking in the relationship to glucose metabolism.

Conclusion

Experimental and clinical studies confirm negative effects of smoking on the beta cells: both by impaired insulin secretion and by changes related to beta-cell apoptosis associated with prediabetes and diabetes. Several mechanisms in the effects of nicotine and cigarette smoking extracts have been elucidated. Increased oxidative stress within the cells posessing the nicotine receptors may explain reactions worsening beta-cell function and insulin resistence development. Similar changes have been observed in endothelial cells developing dysfunction. In combination of diabetes and smoking the cellular impairment is significantly accelerated and the need for smoking cessation is much more important.

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