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Relationship between *FTO* gene polymorphism, obesity, type 2 diabetes mellitus and cancer risk

Oncodiabetologic correlations

Doctoral (Ph.D.) thesis booklet

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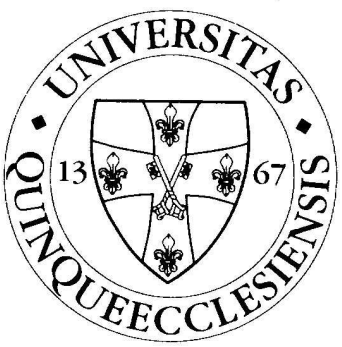

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INTRODUCTION

The professional basis of my thesis were my experience and research findings from my medical practice and studies. My main objective was to investigate and confirm the correlation between obesity, type 2 diabetes mellitus and malignancies at epidemiological, metabolic, molecular genetic and therapeutic levels.

Epidemiological correlations

In the 20th century, obesity, type 2 diabetes (T2DM) and tumors all became endemic illnesses. In 2010, 511 million adults worldwide suffered from obesity. By 2030, it is expected to affect 1 billion people (17.5% of adults). In our country, 31.6% of adults were obese in 2013, that approaches nowadays 33%. In the world, T2DM affected 537 million people in 2021 and responsible for more than 6.7 million deaths. In Hungary today, one in 11 adults has confirmed diabetes mellitus. More than 19 million people were diagnosed with cancer in 2020 and nearly 10 million people died from cancer-related causes. In our country, cancer mortality is currently the second place, but cancer is already the leading cause of years of potential life lost in health.

Metabolic correlations

Obesity, particularly in relation to carbohydrate and fat metabolism, generates further pathological changes. On the one hand, the increase in the proportion of visceral adipose tissue reduces the body's sensitivity to insulin, and on the other hand, the results in a so-called low-grade chronic systemic inflammatory state. The reactive oxygen derivatives damage lipids, proteins and DNA, which may increase the expression of protooncogenes. A number of cytokines produced by tumour cells may play a role in the inappropriate expression of insulin receptors, altered insulin and somatomedin efficacy, and thus induce insulin resistance and reactive hyperinsulinemia. The hyperglycemia that accompanies the insulin resistance facilitates tumour promotion and progression, which is deposited on the mitogenic effects caused by hyperinsulinemia. Persistently high blood glucose levels enhance non-enzymatic tissue glycation with generating advanced glycation end products. Some of these are DNA, cellular and tissue damaging material, others modulate the formation of additional toxic agents. In obesity, prediabetes and diabetes, the balance between the generation and elimination of destructive compounds is capsized, leading to a state of chronic oxidative stress and genome instability.

Molecular genetic correlations

The insulin and IGF1 receptors can be activated by insulin, IGF1 and IGF2 as well, and their effect is that the mitogenic/proliferative signalling pathway RAS and the anti-apoptotic signalling pathway PI3K can come into action. As one of several connections between them, the activated RAS can independently trigger the PI3K pathway. In this case, the simultaneous proliferation and apoptosis inhibitory signals can amplify each other inducing explosive cell proliferation. The RAS pathway and active MAPK/ERK complexes activate nuclear transcription factors that stimulate cell proliferation. These factors are products of protooncogenes, which activating mutations and amplifications may be a part of multistage carcinogenesis. The major mediator of insulin's and somatomedins' metabolic effects is the PI3K pathway. In the presence of glucose, inhibition of AMPK activates mTORC1, however inhibits autophagy. Thus, activation of AMPK may have antitumour effects. With genome-wide association studies (GWAS) today more than 100 gene loci are associated with polygenic obesity. Although the irrespective strength of these genes', including the well-known *FTO*, is not very high, but together they may predict the risk of obesity. More than 400 SNP variants are known to be correlated to the diabetes. Most of the genes have an effect on insulin secretion, while the minority, including *FTO*, affects insulin sensitivity of tissues. By facilitating obesity, many gene-environment interactions may increase the risk of diabetes and thus play a role in the development of malignancies. In this respect, examination of the *FTO* gene is a priority important.

Thrapeutic correlations

All non-insulin antidiabetics (NIAD) have a general anticancer effect by controlling glycemia, and may even have a specific antitumour effect as well. The complex antitumour effect of metformin has been proven in a remarkable amount of malignant tumours. It reduces insulin resistance and has antimitogenic, antiproliferative and apoptosis modulating direct antitumour effects. It activates the products of the *ATM* and *LKB1* tumour suppressor genes and then inhibits the PI3K pathway through stimulation of AMPK, thus inhibiting protein synthesis and cell growth. Stimulates the phosphoprotein p53 and therefore selectively enhances apoptosis and stops cell cycle by acting on cancer stem cells. Facilitates the direct binding of AMPK to the PD-L1 protein, resulting in a downregulation of its expression. In addition, it inhibits the uptake of vitamin B12, which is essential for tumour cell DNA synthesis too.

HYPOTHESES

- Polymorphism of obesity-associated *FTO* gene may play a role in the effects of glucose and triglyceride supply on nutritional status.
- Obesity is an important risk factor for T2DM, which means that *FTO* gene variants may also be risk factors for the development of diabetes.
- Genom-wide association studies may be important in determining risk of disease in individuals for obesity and T2DM.
- The nutritional status of patients suffering from malignant diseases and type 2 diabetes is different from that of other patients suffering from malignancies, because they are more likely to have abnormal changes in BMI in any direction.
- Among patients suffering from malignant diseases, T2DM is likely to manifest more often than in general population.
- The quality of glycemic control in patients, suffering from diabetes and malignancies may affect tumour progression, and metastatic tumour stage may be more common in diabetic patients.
- The aetiological role of T2DM may vary depending on the pathogenesis of the tumour, and thus its incidence may notable differ depending on the origin of primary tumour.
- Metformin has a complex metabolic and antitumour effect, i.e. it may reduce blood glucose level and body weight of patients, suffering from diabetes and malignancies, and/or independently may slow tumour progression and development of metastases.

I. INVESTIGATION

In our study, we analysed the effect of energy and nutrient supply on *FTO*-related obesity in a "gene-environment" model in the light of changes in BMI, and inferred the risk of T2DM. The environmental factors were plasma glucose and triglyceride and the genetic component was the *FTO* gene polymorphism. In addition to multiple measurements of fasting and post-challenge blood glucose levels, fasting triglyceride, and BMI of the subjects, the *FTO* rs9939609 SNP AA/AT/TT genotype was determined in all participants. After that we formed subgroups, based on these parameters and compared them to find statistical relationships between nutrient intake, nutritional status and *FTO* gene polymorphism.

Patients (Material): Subjects were recruited from the TUEF (***Tue****bingen* ***F****amily Study for type 2 diabetes*), and the Whitehall II Study, which analysed mortality data and psychosocial risk factors for cardiovascular and metabolic diseases.

Methods: Calculation of BMI based on body weight and height (kg/m^2). Determination of fasting (FPG) and post-challenge (OGTT) plasma glucose and fasting triglyceride (FTG) levels using an analyser (mmol/l). DNA microarray or chip-based sequencing was used to determine *FTO* genotypes. Statistical analysis of the correlations between study parameters was performed by using linear regression, additive inheritance and linear mixed models.

Results: Baseline data from subjects included in the TUEF and Whitehall II studies are summarised in a table [Table 1].

Study	TUEF (n=2.671)	Whitehall II (n=4.966)	Both (n=7.637)
Sex ratio (female/male %)	64/36	26/74	39/61
Age (year)	41.0 (30.0-52.0)	49,5 (45.0-55.7)	46.5 (30.0-55.7)
Body weight (kg)	85.0 (70.7-103.4)	75.1 (67.2-83.2)	78.6 (67.2-103.4)
BMI (kg/m^2)	28.5 (24.2-35.7)	24.8 (22.8-27.0)	26.1 (22.8-35.7)
Fasting plasma glucose (FPG, mmol/l)	5.2 (4.8-5.6)	5.2 (4.9-5.5)	5.2 (4.8-5.6)
Fasting triglyceride (FTG, mmol/l)	1.15 (0.8-1.7)	1.16 (0.8-1.7)	1.16 (0.8-1.7)
***FTO rs9939609* AA/AT/TT genotypes ratio (%)**	32/50/18	36/48/16	34/49/17

Table 1 | Baseline data from the TUEF and Whitehall II clinical studies.
[Median, interquartile ranges and percentages are shown.]

In TUEF participants, genetic variation in *FTO* was strongly associated with BMI ($p<2x10^{-10}$), even after correction for sex and age ($p<3x10^{-10}$), and the strength per risk allele was 1.7±0.3 kg/m^2. Polymorphism of the *FTO* gene showed a significant interaction with fasting blood glucose levels, following variation in BMI, both with and without adjustment for FTG ($p<0.001$). In subjects with the rs9939609 AA risk genotype an increase in FPG per mmol/L resulted in a BMI 1.8±0.7 kg/m^2 higher than in individuals with the TT genotype. Fasting triglyceride levels were also associated with *FTO* alleles in both the presence ($p<5x10^{-8}$) and absence ($p<5x10^{-4}$) of FPG. In the presence of the AA risk genotype, an increase in FTG per mmol/l increased value of BMI by 2.1±0.5 kg/m^2 compared to the TT genotype. Similar correlation has not been confirmed between *FTO* genotypes and plasma glucose levels after OGTT ($p>0.05$) [Figure 1].

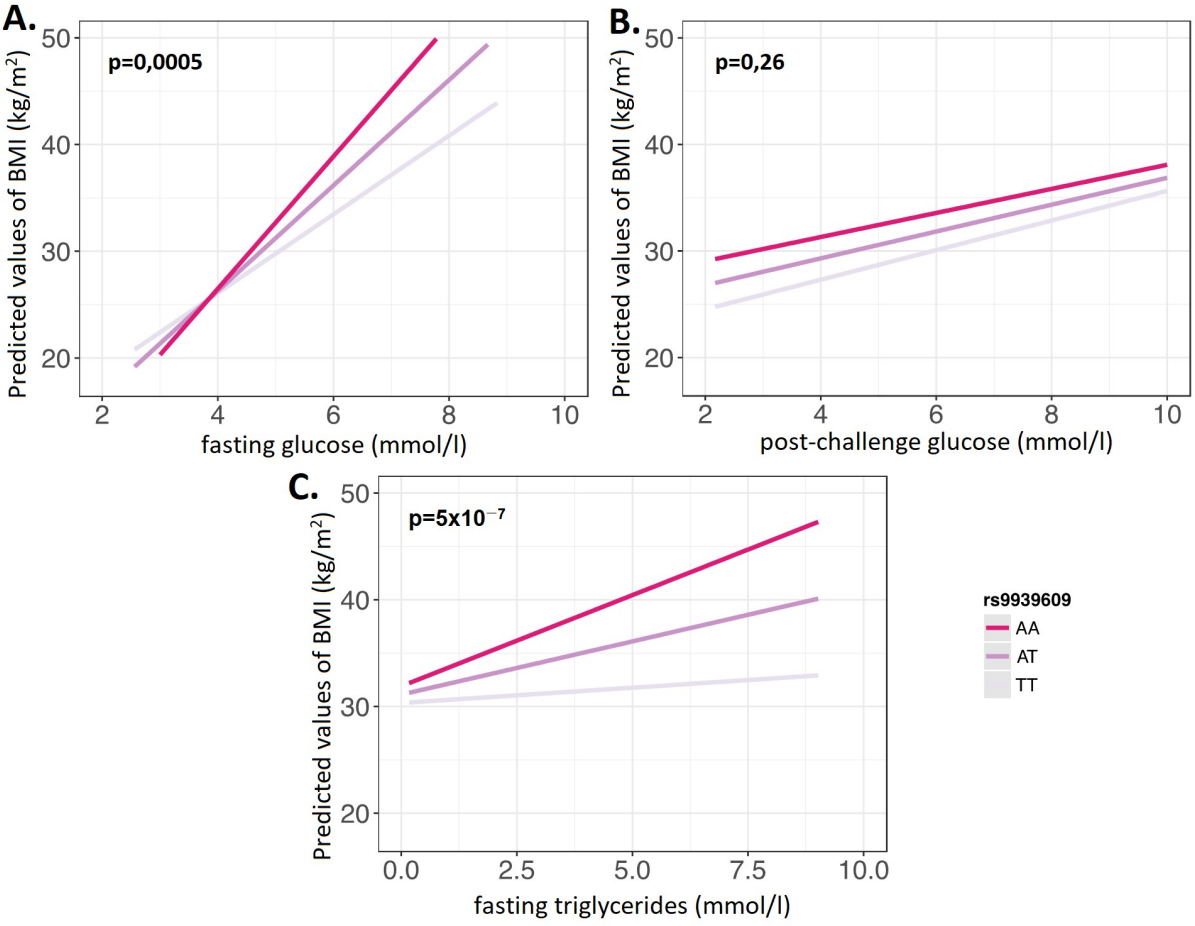

Figure 1 | Changes in BMI depending on plasma glucose and triglyceride levels. *[Linear regression models plotting the predicted values of BMI against fasting (**A**), post-challenge (**B**) glucose and fasting triglycerides (**C**) in interaction with the FTO SNP rs9939609 in the TUEF study. Colours indicate FTO genotypes. The p-values are given for the respective interaction terms in models adjusted for sex, age, and either fasting glucose or triglycerides.]*

Among the Whitehall II Study subjects, BMI proved to be highest for the *FTO* rs9939609 AA gene variant and lowest for the TT variant. FPG depending on BMI variation showed a significant association with the number of *FTO* gene variants at risk ($p<0.05$), which translated into a 0.2% increase in BMI per risk subject for a 1 mmol/l increase in FPG. Comparison of the lowest and highest mean FPG quartiles showed that mean FPG modulated the effect of *FTO* genotypes on BMI over the entire follow-up period ($p<0.05$). It was supported by the fact that those participants, with higher mean FPG and carrying the *FTO* risk allele "A" showed greater weight gain [Figure 2].

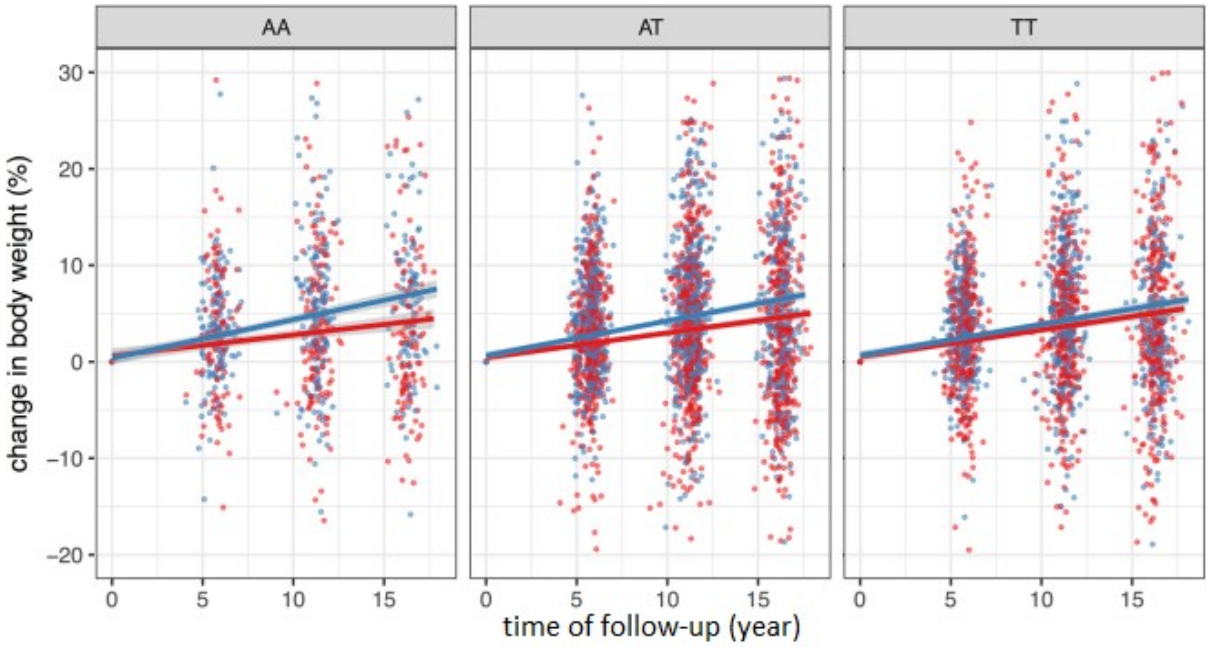

Figure 2 | Interaction effect of glycemia and FTO rs9939609 on change of body weight. *[Panels show weight gain of participants carrying different FTO rs9939609 genotypes in the WH II cohort. Colours indicate quartiles of average FPG per subject and populations over the full follow-up period (red: bottom quartile, 4.1-4.9 mmol/l, blue: top quartile, 5.4-16.0 mmol/l) with 95% CI.]*

Discussion: Both studies demonstrated in an independent cohort that fasting blood glucose and *FTO* gene variations interact, causing changes in body weight and increasing BMI. It is hypothesized that gene-environmental interactions may contribute significantly to the inheritance of diseases, first of all metabolic changes, such as metabolic syndrome, obesity, insulin resistance, T2DM, which are not yet explained by genetics, and there is even more evidence for their role in the development of malignancies. The interaction between plasma glucose and *FTO* gene, as we have demonstrated, may be due to several biological mechanisms. *FTO* variations, through the products of genes *IRX3* and *IRX5*, may have significant

effects on adipocyte function, energy use, production and storage. Increased expression of IRX3 and IRX5 transcription factors leads to autonomous changes during development and differentiation of adipocytes, which - in the end - may result in a phenotype that promotes increased lipid storage and reduces thermogenesis-induced energy loss. The oversupply of energy and nutrients may therefore also enhance the effect of *FTO* genotype on obesity.

Like us, others have found increased caloric intake in carriers of the *FTO* risk allele. In accordance with that, there is more and more evidence that *FTO* is one of the highest expressed genes in the central nervous system, and its variability affects the function of appetite centre and the insulin sensitivity of cerebral cortex. The appetite dysregulation and cortical insulin resistance associated with *FTO* risk alleles may contribute to the close relationship between glucose availability and BMI changes. These processes interact with the dopaminergic system too, as the human brain's genetically determined dopamine receptor density further modulates the obesityogenic effect of the *FTO* gene. Physiologically, elevated blood glucose suppresses appetite and reduces food intake. This balance is shifted by the association between *FTO* variation and brain activity, which becomes more pronounced with increasing glycemia. Thus, persistent hyperglycemia may amplify the effect of the *FTO* gene polymorphism on body weight via the brain too.

Confirmed that both glycemia and triglyceridemia can interact with the *FTO* gene, resulting in changes in body weight, our study provides further evidence for the importance of gene-environment interactions in the pathogenesis of obesity. Although the biological mechanism of these interactions is not clear from our data, our results suggest that nutrient-excess, in individuals with higher fasting blood glucose level, increases the risk of weight gain further, in case of presence of the AA genetic variant of the *FTO* gene. As weight gain accelerates deterioration of metabolic status forth, this association leads to a vicious circle of more severe obesity and increased risk of T2DM as well. Therefore, effective pharmacological and non-pharmacological antiglycemic strategies may be necessary to achieve metabolically balanced weight loss, especially in individuals suffering from prediabetes or type 2 diabetes and with risk allele of *FTO*.

II. INVESTIGATION

In our workplace cohort study, our aim was to confirm the epidemiological and metabolic connection between obesity, T2DM and malignant diseases classified by site of the primary organ and stage of extension. Besides that we investigate the therapeutic correlations of these pathologic states, particularly regarding to the emerging antineoplastic efficacy of metformin, based on our experience too. Since, at the time of our study, the use of metformin in patients with malignant neoplasms without concomitant diabetes was considered as off-label trial, we were restricted to a retrospective analysis of data from diabetic patients suffering from malignant diseases, treated with metformin and to a synthesis of epidemiological and experimental research data and literature information on the relationship between metformin and oncogenesis.

Patients (Material): We reviewed the medical history and treatment of 1.224 adult patients treated in the Oncology Centre of the Pándy Kálmán Hospital of the Central Hospital of Békés County through the analysis of data extracted from medical records, bed headboards and hospital IT systems.

Methods: BMI calculated from hospital registration parameters (kg/m^2). Ranges: BMI<18.5 kg/m^2 (malnourished status, underweight), 18.5≤BMI<25.0 kg/m^2 (normal nutritional status, healthy weight), 25.0≤BMI<30.0 kg/m^2 (preobesity, overweight), BMI≥30.0 kg/m^2 (obesity), BMI≥25.0 kg/m^2 (overweight obesity). Admission plasma glucose (APG) determined by central laboratory automation (mmol/l). Ranges: APG<3.5 mmol/l (hypoglycemia), 3.5≤APG≤11.0 mmol/l (normoglycemia), APG>11.0 mmol/l (hyperglycemia). For technical reasons, only percent (%) ratios were calculated in data processing, using a two-sample T-test, chi-square test and one-way analysis of variance (ANOVA) at the 5% significance level (p=0.05).

Results: The mean age of the study patient population was 62.9±10.4 years, and females were significantly older (p<0.001 vs males). Although the female : male ratio (49.5% vs 50.5%) differed from that, observed in the adult population (53.2% vs 46.8%), the proportion of patients aged 60 years and over (62.8% vs 62.6%) was similar. Key data for the patients studied are summarised in a table [Table 2].

Investigated subjects	Male (n=618)	Female (n=606)	Both (n=1.224)
Age (year)	61.6 (51.1-72.1)	64.1 (54.1-74.2)	62,9 (52.5-73.2)
BMI (kg/m^2)	26,2 (21.3-31.0)	27.0 (21.0-33.1)*	26.6 (21.1-32.1)
Admission plasma glucose (APG, mmol/l)	6.6 (3.8-9.5)	6.7 (4.2-9.3)**	6.7 (4.0-9.4)
Obesity range (%)	19.9	26.7$^{\#}$	23.3
T2DM range (%)	19.4	21.3$^{\#\#}$	20.3
Range of metastasis (%)	48.2	63.4	55.7

Table 2 | General characteristics of the study population.
*[Median ranges and percentages are shown.][*The mean BMI was higher in women (p<0.01 vs men), but they may have a higher proportion of subcutaneous obesity, which is less of a burden of cancer risk. **No significant gender difference was confirmed for mean APG. $^{\#}$Women had a higher rate (p<0.01 vs men) and more severe (34.8±4.2 vs 33.0±3.0 kg/m^2, p<0.001 vs men) obesity. $^{\#\#}$For women, the prevalence of T2DM was not significantly different (p>0.05 vs men).]*

In the total studied population, the prevalence of obesity was 23.3%, lower than the prevalence 31.6% in the adult population. The prevalence of obesity was 20.7% (vs 31.0%) in the 40-49 age decade, 23.7% (vs 37.6%) in the 50-59 age decade, 29.6% (vs 40.9%) in the 60-69 age decade, and 17.5% (vs 35.4%) in the over 70 age decade [Figure 3].

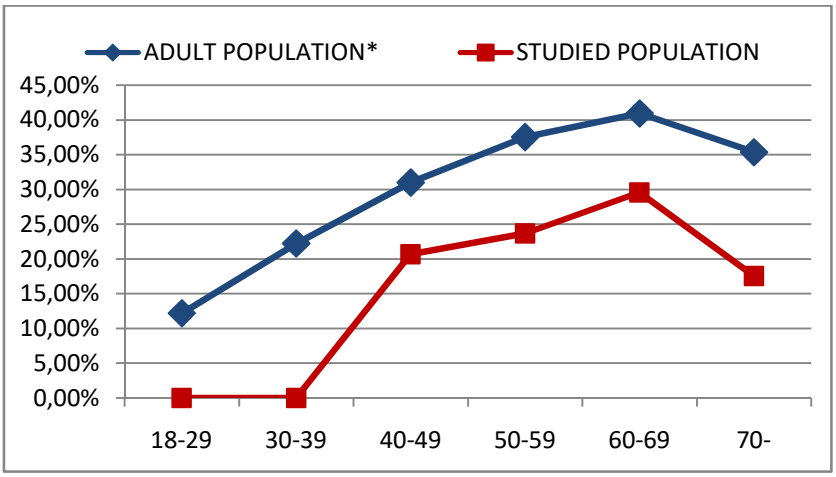

Figure 3 | Proportion of obesity by age decades.
*[*Rurik, et al. A public health threat in Hungary: obesity, 2013. BMC Public Health. 2014/ Hungarian Central Statistical Office 2013. www.ksh.hu/interaktiv/korfak/orszag.html]*

The prevalence of T2DM was found to be 20.3%, higher than the currently known prevalence of 6.4% in the adult population. The epidemiological link between diabetes and cancer risk was clearly supported by a comparison of diabetes prevalence by age decades. The prevalence of T2DM was 6.9% (vs 4.5%) among

41-50 years old, 17.5% (vs 12.8%) among 51-60 years old, 21.8% (vs 19.0%) among 61-70 years old, and 26.3% (vs 20.0%) among the over 70 years old [Figure4].

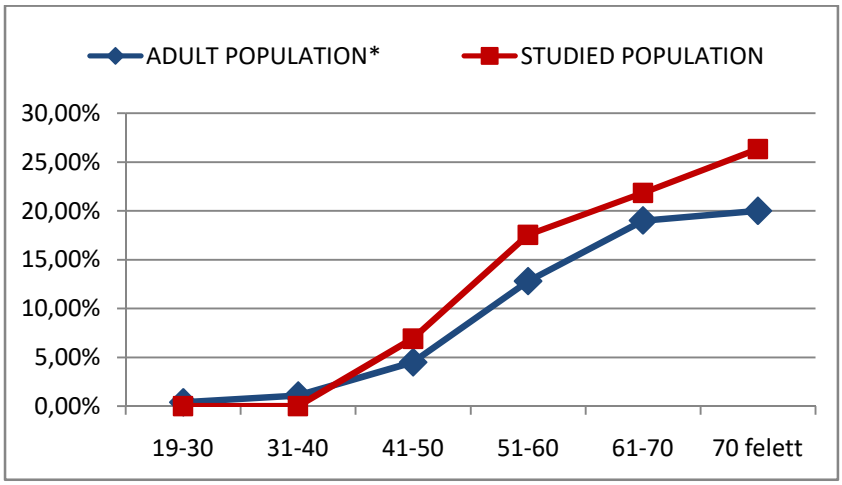

Figure 4 | Proportion of type 2 diabetes by age decades.
*[*Kempler, et al. Prevalence and financial burden of type 2 diabetes in Hungary between 2001-2014. Diabetol Hung. 2016]*

In normal nutritional status and overweight obesity, the rates of dissemination were higher (57.1% and 56.4% vs 38.1%, p<0.01 vs BMI<18.5 kg/m^2) and markedly higher in the presence of pronounced obesity (64.6% vs 53.0%, p<0.001 vs BMI<30.0 kg/m^2). Tumour progression was accompanied by an increase in plasma glucose levels (7.1±3.3 vs 6.1±1.6 mmol/l, p<0.001 vs METAST-) and a higher proportion of patients with hyperglycemia had metastatic stage (91.0% vs 53.3%, p<0.001 vs APG<11.0 mmol/l). During adjuvant and neoadjuvant oncotherapy, in tumour stages I-III, a much lower rate of glucometabolic disturbance; hyperglycemia (4.0% vs 19.7%, p<0.001 vs PALL) or T2DM (16.1% vs 25.5%, p<0.001 vs PALL) could be observed.

Searching an epidemiological link between T2DM and cancer, we also examined the prevalence by primary organ of origin in diabetic versus non-diabetic patients. In both subgroups, colorectal carcinoma was ranked first and postmenopausal breast cancer second. In diabetic patients, pancreatic, ovarian, bladder, prostate and primary hepatocellular cancers were observed next. Looking at the prevalence of T2DM by tumour site, 60% of patients suffering from hepatocellular carcinoma, half of patients with pancreatic, bladder, prostate and endometrial cancer, 40% of melanoma patients and one third of renal cell cancer patients had diabetes, followed by postmenopausal breast, ovarian, gastric and rectal carcinomas [Table 3].

Localisation of tumour (n=number of patients)	T2DM range (%)	P-value**	Link between tumour and T2DM[#]
Liver (15)	60.0	< 0.001	+++
Pancreas (30)	50.0	< 0.001	+++
Bladder (30)	50.0	< 0.001	+++
Prostate (18)	50.0	< 0.002	+++
Endometrium (12)	50.0	< 0.02	+++
Skin /melanoma/ (15)	40.0	> 0.05	++
Kidney (18)	33.3	> 0.05	++
Female breast /age≥60 year/ (120)	30.0	< 0.006	+++
Ovary (60)	25.0	> 0.05	++
Female breast /total/ (183)	23.0	> 0.05	++
Stomach (27)	22.2	> 0.05	++
Rectum (216)	22.2	> 0.05	++
All patients (1.224)	20.3	na.***	+
Colon and rectum (564)	18.6	> 0.05	+/-
Lung (33)	18.2	> 0.05	+/-
Colon (348)	16.4	> 0.05	+/-
Female breast /age<60 év/ (63)	9.5	> 0.05	+/-
Home adult population*	6.4*	na.***	na.[##]
Head and neck (102)	5.9	> 0.05	-/-

Table 3 | Type 2 diabetes prevalence by primary tumour location.
*[Percentage rates and p-values of two-sample T-tests are indicated.][*Kempler, et al. Prevalence and financial burden of type 2 diabetes in Hungary between 2001-2014. Diabetol Hung. 2016. **This value indicates whether the diabetes rate between the given tumour group and the rest of the study population (quasi-control group) is really different. ***P-value can't be given. [#]Assessment of association between malignancies and T2DM as follows: **+**: diabetes rate above the literature value in the total adult population/diabetes rate above the value calculated for the total study population/p-value supporting a significant difference, **-**: diabetes rate below the literature value in the total adult population/diabetes rate below the value calculated for the total study population. [##]No corresponding data.]*

In order to identify therapeutic implications, we also analysed the relationship between APG, BMI and tumour stage according to the form of non-insulin antidiabetic medication. All of the antidiabetic agents control glycemia and thus may have indirect antitumour effect. This is supported by the fact, that in all subpopulations receiving

NIAD agents, the mean APG was found to be lower, than in diabetic patients, who do not receive non-insulin antidiabetics. The rates of metastasis in diabetic patients receiving and not receiving NIAD therapy did not differ significantly, regardless of whether the former patients' antidiabetic therapy included metformin or not. The breakthrough study was that of those patients, taking metformin monotherapy, who had a significantly lower, around 40% rate of metastatic stage, compared to the non-diabetic and any diabetic subgroups ($p<0.001$ vs T2DM+/NIAD-, $p<0.05$ vs NIAD+/MET-, $p<0.01$ vs NIAD+/MET+). In addition, we observed an interesting phenomenon, that metformin-treated (NIAD+/MET+) patients, based on APG values, were clinically clustered into two subpopulations [Figure 5].

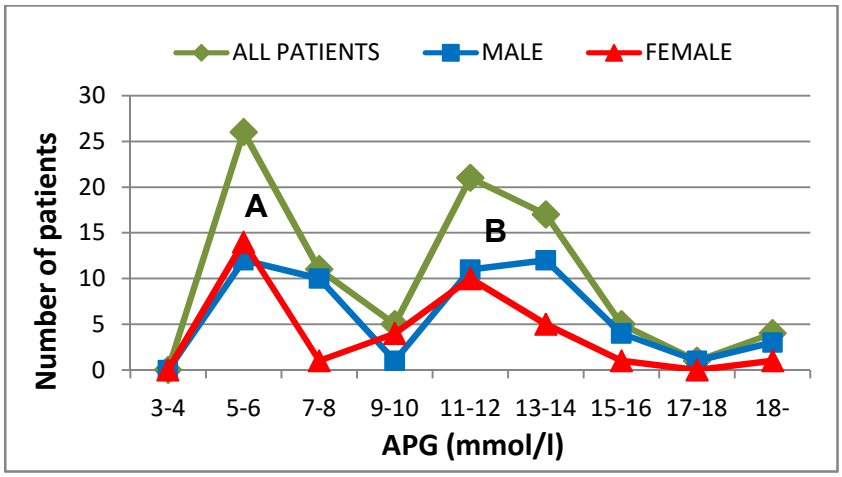

Figure 5 | Distribution of blood glucose levels in diabetic patients treated with metformin and suffering from cancer.
*[Groups of patients with (**A**) lower (5.0<APG<10.0 mmol/l) and (**B**) higher (APG>11.0 mmol/l) admission plasma glucose levels.]*

In the subgroup with the more favourable phenotype "A", those on combination metformin treatment (63.2% vs 33.3%, $p<0.01$ vs "B") predominated, where as in subpopulation "B", those on metformin monotherapy (66.7% vs 36.8%, $p<0.01$ vs "A") were predominant. The mean BMI of patients with the less favourable phenotype "B" was lower, not significantly, but lower (28.6±4.2 vs 30.1±4.8 kg/m^2, $p>0.05$ vs "A"), and included a higher proportion of patients on palliative therapy (75.8% vs 54.4%, $p<0.05$ vs "A"). This was in line with the higher metastasis rate observed in their cases (84.6% vs 52.9%, $p<0.01$ vs "A").

Discussion: In the studied population of patients suffering from cancer, the rate of obesity was lower (23.3% vs 31.6%) and the prevalence of diabetes was higher (20.3% vs 6.4%) compared to the adult population. In case of obesity and T2DM, the

risk of developing several tumours is increased, and disorders of carbohydrate metabolism and changes in nutritional status are more common in patients suffering from cancer. Compared to the average population, our patients had a higher incidence of T2DM, especially in case of primary hepatocellular carcinoma, pancreatic, bladder, prostate, endometrial and postmenopausal breast cancer. In contrast to these tumours, minor role of diabetes and major role of other aetiological factors are featuring most of the tumours associated with low diabetes rates and common in non-diabetics. The different glucometabolic behaviour of pre- and postmenopausal breast cancers refers to that, we observed 9.5% of cases of diabetes in people under 60 years of age, and 30.0% in older people.

Obesity is a risk factor for T2DM and a catalyst for tumour progression, which was confirmed by our results as well, as both the proportion of patients with diabetes and metastatic stage increased by higher BMI. In metastatic disease, the minimally higher BMI may primarily refer to pseudoobesity, due to water retention, sarcopenia and other factors that often accompanied by tumor progression. The high rate of diabetes in patients suffering from cancer with normal nutritional status may be an indication of an obesity-independent risk role of diabetes. In cancer patients with diabetes, despite the anorexia-cachexia syndrome, we observed a higher proportion and more severe overweight or obesity and calculated a significantly higher BMI. In this case, a higher BMI is generally not the sign of a really improved nutritional status, which is a better prognosis, because the metabolic and immunological changes that accompany diabetes also place a burden on the organisation suffering from cancer. The consequent spread of metastases ultimately leads to cachectic changes, the opposite of obesity. All this may be due to metabolic features of T2DM.

In palliative oncotherapy, we observed an increased incidence of diabetes, supported by the clinical relevance of growing tumour and cytostatic-induced secondary diabetes. In related data, 15.7% (n=39) of diabetic patients studied, were diagnosed with diabetes during oncological therapy. Metastatic patients had a higher rate and more severe form of hyperglycemia or diabetes mellitus, and metastatic stage was more frequently observed in hyperglycemia and T2DM. The close association may suggest a modulating role of diabetic metabolism in oncogenesis and an adverse effect of cancer progression and oncotherapy on glucometabolism. However, in

patients with diabetes mellitus, a too strict control of glycemia is not always beneficial, as lower blood glucose levels are not always associated to moderate tumour progression.

The role of metabolic medicines in cancer treatment has been investigated for a long time. In our study, we primarily looked for evidence for the antitumour effects of metformin. Our results showed that highest BMI value could bed detected among metformin users, which may be due to the fact that it is still the first choice of antidiabetic medicines in overweight or obese diabetic patients. In our analysis, among metformin takers was found to have the lowest rate of metastatic tumour stage, while APG and BMI were the highest. This further demonstrates that the antimetastatic effect of metformin may be complex, as it may not provide adequate glycemic and weight control at the same time, which is problematic in patients with cancer and diabetes, as therapeutic inadequacy of antidiabetics may be induced by both insulin resistance, caused by biologically active tumours and diabetogenic side effects of cytostatics. One reason could not be given to explain the separation of metformin-treated patients into glycemic subpopulations, as several independent factors could be found in the relationship between subgroups.

Based on our results, when screening diabetic patients for malignant diseases or investigating for symptoms refer to carcinomas, a screening for colorectal, breast, pancreatic, bladder, prostate, renal, endometrial, ovarian and primary hepatocellular carcinoma is professionally recommended. Pathological glucometabolism is a major risk factor for the development of these tumours, and appropriate control of diabetes mellitus may improve the effectiveness of their prevention. In addition, in view of the increased risk of T2DM, following the diagnosis of primary hepatocellular, pancreatic, bladder, prostate, endometrial and postmenopausal breast cancer, the search for possible underlying latent carbohydrate metabolic disorders and appropriate therapy is recommended, with particular reference of metformin preference.

THESES, RECENT FINDINGS AND RESULTS

- Gene-environment interaction is important in the pathogenesis of obesity. Alterations in nutrient availability affect body weight through the *FTO* gene polymorphism, as it correlates well with BMI, thus acting on the risk of T2DM.

- The risk allele „A" carriers of the genotypes of the *FTO* rs9939609 SNP variants show an association with BMI, as their presence is associated with significant weight gain at higher plasma glucose and triglyceride. Both higher numbers of the „A" allele and higher nutrient availability lead to more significant weight gain.

- As our genotyping procedures are also the technical basis for gene association analyses, the use of GWAS may have practical relevance in determining individual disease risk, especially in illnesses that are polygenic inherited.

- In case of T2DM, overweight and obesity affect patients suffering from cancer more, and in diabetic patients, dissemination is more pronounced, which in turn favours cachectic changes, oppositely to obesity.

- Obesity modulates the development of T2DM and tumour progression, as the rates of both diabetes and metastatic stage increase with increasing BMI. The higher rate of diabetes among patients suffering from cancer with a normal BMI indicates that T2DM is a cancer risk independent of obesity.

- Glycemic control is notably worse in dissemination and palliative oncotherapy, as hyperglycemia or diabetes is then more frequent and more severe. All this confirms the clinical relevance of secondary diabetes.

- Patients suffering from T2DM have a higher incidence of colorectal, breast, pancreatic, liver, bladder, prostate, renal, endometrial and ovarian cancer, and a significantly higher incidence of diabetes can be detected in patients with liver, pancreatic, bladder, prostate, endometrial and postmenopausal breast cancer.

- Metformin has been proved to have a complex antitumour effect, which may prevail independently from glycemia and body weight. Using it as monotherapy, the lowest rate of metastatic stage could be detected compared to other antidiabetics, despite of being associated with the highest BMI and glucose level.

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"Scientia aeterna est, homo transiens."

(Science is eternal, man is transient.)