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Moderate Exercise, Weight Reduction and Oxidative DNA Damage in Cancer Risk Groups

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Abstract

Patients with obesity and/or type 2 diabetes have an increased tumor risk including colorectal cancer. Physical activity, exercise and weight reduction programs are effective strategies to decrease this risk. Highly sensitive tumor risk biomarkers modifiable by lifestyle factors such as oxidative DNA damage products (8-oxo-2'deoxyguanosine [8-oxo-dG]) increasingly are used in epidemiologic and clinical intervention studies to better quantify this risk. Epidemiologic and intervention trials have shown that systemic 8-oxodG concentrations are increased in a variety of disorders and diseases such as obesity and type 2 diabetes. Most studies found a decrease of 8-oxo-dG following exercise with moderate intensity, but an increase after high intensity programs suggesting a hormesis relationship between urinary 8-oxo-dG excretion and the intensity levels. The relationship of 8-oxo-dG concentrations with body mass index (BMI), however seems to be less consistent. Starting from data of clinical intervention studies assessing the different effects of graded exercise (from very moderate to submaximal intensity) on fat metabolism in lean and obese individuals the scope of this minireview is to give clinically practicable support to design appropriate biomarker-monitored intervention programs for patients at increased cancer risk such as patients with obesity and type 2 diabetes.

Keywords: Type 2 diabetes; Obesity; Colorectal cancer risk; Weight reduction; Physical activity; Graded exercise intensity; Oxidative DNA damage; 8-oxo-dG

Abbreviation: CRC: Colorectal Cancer; T2D: Type 2 Diabetes; ATP: Adenosine Triphosphate; BMI: Body Mass Index; EX: Exercise; FA: Fatty Acids; PA: Physical Activity; 8-oxo-dG: 8-Oxo-2'-Deoxyguanosine; VO 2max: Maximal Oxygen Uptake

Cancer Risk, Lifestyle Aspects and Oxidative DNA Damage (8-oxo-dG)

The call for moderation originally inscribed on the temple of Apollo in Delphi, Greece, first appears in P. Terentius Afer's comedy Andria and has attracted many philosophers and writers throughout centuries (https://www.ne quid nimis/Wikipedia). It was not until very recently that medical science placed this behavioural norm on a more evidence-based level.

Epidemiologic and clinical studies over the last three decades have convincingly demonstrated that patients with metabolic disorders particularly those with an elevated body mass index (BMI [kg/m2]) and/or those with type 2 diabetes (T2D) have a higher overall tumor risk including breast and colorectal cancer (CRC) in the range of 30 to 40 percent compared to healthy controls [1-4]. In a recently published meta-analysis compiling data from several large-scale trials with >3 million people and >37,000 cases this risk was quantitated with an increase of 6.0 % per each 5 units increase of BMI: visceral fat mass being a major contributing factor [3,5]. Modification of lifestyle aspects based on weight reduction and/or physical activity programs are established therapeutic modalities to effectively reduce the overall cancer risk including breast cancer and CRC. In addition, weight loss was found to reduce colorectal inflammation and may, thus further contribute to a lower cancer risk [6]. A recent longitudinal study in morbidly obese patients showed a mean reduction of this risk in the range of -3.0 to -10.0 % per BMI unit following laparoscopic gastric band application [7].

Physical activity and exercise (PA/EX) were demonstrated to be associated with a lower cancer risk including CRC in a dose-dependent and inverse relationship ranging from 30 to 50 percent in the more active individuals [8]. To further quantify the

individual tumor risk a series of highly sensitive risk biomarkers modifiable by lifestyle factors (diet,PA/EX) have been proposed, among them 8-oxo-2'-deoxy-guanosine (8-oxo-dG) which was shown to reflect (mutagenic) oxidative DNA damage deriving from interactions with reactive oxygen species produced in excess as a consequence of increased endogenous and exogenous oxidative stress factors [9,10]. Elevated levels of 8-oxo-dG have been found in many conditions and diseases with an increased cancer risk including obesity and T2D [9-15]. In a recently published cross-sectional clinical study comparing urinary 8-oxo-dG excretion in individuals with different CRC-risks we found that urinary excretion in patients with T2D (having a moderately elevated CRC risk) was significantly higher compared to non-diabetic controls (average risk) confirming the observations of these studies but was lower compared to those with curatively treated CRC (high risk for recurrence) [16]. Starting from a basic understanding of beneficial effects of weight reduction and graded exercise on carbohydrate and fat metabolism in target tissues and the quantitative relationship of the intensity of PA/EX with the levels of tumor risk biomarkers such as 8-oxo-dG the scope of this minireview is to discuss clinical and practical aspects to further improve existing education and intervention programs in patients at risk, particularly obesity and T2D.

Graded Moderate Exercise and Carbohydrate/Fat Metabolism

Experimental and clinical evidence over the last two decades has provided a deeper insight into the underlying molecular mechanisms of action and the regulation of the carbohydrate and fat metabolism following different intensities of exercise [17-20]. It is widely accepted that at low to moderate intensity exercise (45.0 – 65.0% of the maximal oxygen uptake [VO2 max]) muscle cells predominantly gain their energy (ATP) from ß-oxidation of fatty acids (FA) derived from different sources such as triglyceride lipolysis in fat adipocytes, intramuscular triacylglycerol stores, FA transport from the blood compartments to muscle sarcoplasm and mitochondrial membrane, whereas ATP production from carbohydrate (glucose) oxidation is downregulated [18,19]; from around 50% VO2 max onwards glycogenolysis from intramuscular glycogen storages starts to be activated (anaerobic conditions), at >70% VO2 max glucose oxidation is the main energy source with downregulation of FA oxidation [18-20]. Although in the majority of these trials healthy volunteers and/or trained athletes have been studied and compared with less active individuals most of this knowledge will be applicable also in clinical settings, when patients at risk are offered appropriate education and biomarker-monitored intervention programs.

Body Mass Index, Weight Reduction and Oxidative DNA Damage (8-oxo-dG)

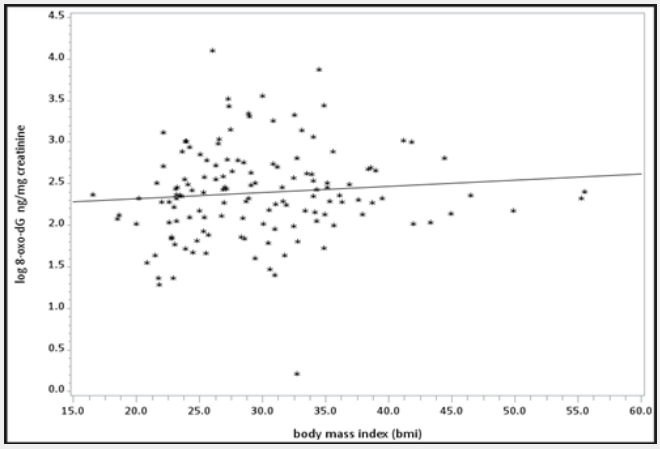

Figure 1: Correlation of body mass index (BMI)(X-axis) and urinary 8-oxo-dG excretion (Y-axis) in participants (N=137) of our recent study [16].

Data concerning BMI and the levels of DNA damage products seem to be contradictory at a first glance as studies reporting inverse (negative) as well as positive or no correlation have been published [7,21-24]. Thus, in a longitudinal study investigating a cohort of 179 healthy office workers a negative correlation up to BMI 27 kg/m^2 was found [23]. In contrast, in morbidly obese patients undergoing bariatric surgery a positive correlation was observed with a highly significant decrease of urinary excretion of 8-oxo-dG (-1.12 ng/mg creatinine/unit BMI) six months after surgery [7]. Based on their data the authors of both groups suggested that there may be a negative correlation at low/normal BMI (<27 kg/m^2) turning positive above this value [7,23]. The observation of a positive correlation (p=0.04) in the participants of our study is in accordance with these findings (Figure 1) [16]. However, when data are reanalyzed according to the diagnosis of the participants (T2D, CRC, non-diabetic controls) the observed positive correlation remained significant only in controls with an increase of urinary 8-oxo-dG excretion of approximately +0.1 log

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ng/mg creatinine/per each five BMI units [16]. Additional BMI-models with multiple adjustments for the cofactors gender, age, BMI, alcohol consumption and smoking status yielded similar results [16]. In line with this data are results of an earlier study showing no significant correlation of BMI with urinary 8-oxodG excretion in CRC-patients [25]. It is, therefore, important to define the targeted patient's groups in terms of their diagnosis and adjust for multiple additional confounding factors, when biomarker-monitored epidemiologic and/or intervention programs are planned in patient groups at risk such as morbidly obese individuals and/or those in whom bariatric surgery is planned.

Moderate Physical Activity/Exercise and Oxidative DNA Damage (8-oxo-dG)

Quantitative data concerning beneficial effects of PA/EX on the individual tumor risk in terms of risk biomarkers are clinically important, but not yet widely available in clinical practice and, in addition, not entirely consistent. In contrast to BMI trials, the great majority of clinical and experimental intervention trials in healthy volunteers as well as in patients belonging to CRC-risk groups such as obesity, T2D or curatively treated CRC have shown decreased systemic and urinary 8-oxo-dG levels (and other risk biomarkers) in the range of 20–30 percent following exercise with moderate intensity, whereas at higher intensity levels oxidative DNA damage increased strongly suggesting a hormesis relationship [26-40]. One possible explanation for this effect may be that at moderate levels of exercise intensity (30–50%VO2max) cellular and humoral compensatory mechanisms such as exercise-induced activation of antioxidant defenses (e.g. superoxide dismutase, DNA repair systems) are activated leading to decreased oxidative stress associated with multiple health benefits, whereas at higher EX intensities a shift to more prooxidant compounds may be observed with exhaustion of the compensatory mechanisms with subsequent DNA damage [34-37,39]. In a recent clinical study Dimauro et al. [29] found a small increase of DNA repair capacity of 1.6% per each +7.5 MET-h after moderate exercise, Hofer et al. [24] observed a decrease of oxidative DNA damage in white blood cells from patients following caloric restriction or moderate exercise after 1 year in the range of -48.5 and -49.6 %, respectively, corresponding to a decrease of -0.20 8-oxo-dG/106 d-guanosine per each percent decrease of BMI as calculated from their data. In a study comparing healthy lifelong active men with inactive individuals DNA methylation was significantly lower in 714 promotor regions compared to their inactive counterparts including genes which encode pathways of muscle function, energy metabolism and oxidative stress resistance [38]. Although the contribution to beneficial effects of weight reduction or EX in terms of measurable decreases of 8-oxo-dG per unit BMI or MET-h is rather small, it nevertheless further supports the basic concept that tumor risk biomarkers can be modified by lifestyle factors. In our recently published clinical cross-sectional study [16] we found that urinary 8-oxo-dG excretion was independent of the individual level of PA in the study participants, an observation being somewhat surprising and in contrast to data from interventional studies mostly showing clear beneficial effects of regular exercise on genome stability and DNA damage in risk groups such as patients with T2D [29,31]. A possible explanation of this discrepancy may be that exercise-induced changes of 8-oxo-dG levels are closely linked to rapid changes of humoral and cellular redox systems [36,37] and that these rather short lived effects may have been missed in non-interventional settings such as our study, a view based on a closer look into the time protocols of these studies e.g. times at which biomarkers had been assessed in relation to previous PA/EX [16].

Clinical Aspects of Individually Tailored Exercise Programs

Starting from beneficial health effects of moderate exercise particularly in terms of weight loss and cancer (CRC) risk reduction (quantitatively assessed with risk biomarkers such as urinary 8-oxo-dG excretion) it is important for clinical settings to design biomarker-monitored exercise programs with individually tailored moderate intensity. Evidence from a series of experimental and clinical studies performed within in the last decade have shown that effects of exercise on fat metabolism (and finally weight reduction) may be different in lean and obese individuals [17-20]. In a recent clinical trial studying obese and lean healthy young patients participating in an inpatient education and rehabilitation program the authors observed that fat oxidation rates (FOR) at an intensity level of 20 to 30% VO2max were higher in obese than lean persons, whereas at an intensity level of 65 to 85% VO2max FOR were higher in the lean individuals [20]. From their data the authors suggest that one of the major reasons for this difference may be a decreased fat mobilisation due to an impaired muscular capacity to oxidize non-esterified fatty acids in obesity and T2D patients [20].

Based on this knowledge and our own experience individualized exercise and education programs are offered to all patients admitted to our Department of Gastroenterology and Metabolism. In obese and T2D patients (BMI >30 kg/m^2) training programs with 30 to 40% VO2 max are prescribed (daily exercise time 20 to 40 min for two weeks as inpatients, then continuation three days/week on an outpatient base with follow-up care by their family physicians). Lean patients (BMI<30 kg/m^2) admitted for rehabilitation after curative primary therapy of CRC are enrolled in similar programs but with an intensity slightly higher than that for the obese/T2D (40–50% VO2max). This approach was based on our previous data showing that a moderate (50 W [30-70], median, range), but not a more intensive level (100 W [80 –150]) is beneficial in terms of a reduction of urinary 8-oxo-dG excretion [25]. VO2max was assessed with the bicycle exercise test with incremental increase of the individual workload under continuous ECG monitoring according to a slightly modified protocol as published earlier [25].

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Conclusions and Recommendations

In this minireview clinically practicable recommendations for an active lifestyle with moderate PA/EX are given to individuals with elevated cancer (CRC) risk such as obese persons and those with T2D based on the presently available evidence based on biomarker-monitored clinical trials to quantitate individual risk. Thus, in patients with a BMI>30 an exercise program of low to moderate intensity (30–40%VO2max) is recommended, whereas in those with a BMI<30 the prescribed intensity should be slightly higher (40-50%VO2max). However, the integration of appropriate risk biomarkers (oxidative DNA damage products like 8-oxo-dG) into routine prevention and intervention programs presently is still hampered by the lack of standardization of different determination methods and the relative scarcity of prospective large-scale and long-term intervention studies [41].

Based on the available evidence as outlined in this minireview the author believes that modern medical science strongly supports calls for moderation as they have been present in many philosophies throughout the world for centuries.

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