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Physical Activity, Exercise, Weight Reduction and Oxidative DNA Damage in Colorectal Cancer Risk Groups. Is there a Hormesis Relationship Between Risk Biomarkers and Lifestyle Factors?

H Allgayer*

Department of Gastroenterology and Oncology, Klinik Hartwald, Rehazentrum Bad Brückenau, Germany

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***Corresponding author:** H Allgayer, Department of Gastroenterology and Oncology, Klinik Hartwald, Bad Brückenau Schlüchtener Str.4 DE 97769 Bad Brückenau, Germany

Abstract

Patients with obesity and/or type 2 diabetes have an increased tumor risk including colorectal cancer. Physical acrtivity (PA), exercise (EX) and weight reduction (WR) are effective strategies to decrease this risk. Highly sensitive tumor risk biomarkers such as oxidative DNA damage products (8-oxo-2'deoxyguanosine [8-oxo-dG]) increasingly are used in epidemiological and clinical (intervention) studies to better quantify this risk and to investigate potential effects of PA/EX/WR on this biomarker with the aim to further improve prevention and patient management programs. Based on the available data a U-shaped relationship between urinary 8-oxo-dG excretion and the level of PA/EX intensity is assumed, on the other hand, the relationship with BMI seems to be less clear. In this minireview this data will be discussed with regard to clinical and epidemiologic aspects.

Keywords: Type 2 diabetes; Obesity; Colorectal cancer; Weight reduction physical activity; Exercise; Oxidative DNA damage; 8-oxo-dG

Abbreviations: T2D: Type 2 Diabetes; CRC: Colorectal Cancer; BMI: Body Mass Index; PA/EX: Physical Activity/Exercise; 8-oxo-dG: 8-oxo-2'-Deoxy-Guanosine; ROS: Reactive Oxygen Species; ROM: Reactive Oxygen Metabolites; TTL: Total Thiol

Introduction

Epidemiologic and clinical studies in the last three decades have convincingly demonstrated that patients with type 2 diabetes (T2D) have a higher tumor risk including colorectal cancer (CRC) and that CRC-patients with T2D have an elevated risk of a more aggressive disease course compared to non-diabetic individuals [1,2]. In addition, there is convincing evidence that elevated body mass index (BMI [kg/m^2]) particularly visceral fat mass may also contribute to an increased tumor risk including CRC, whereas on the other side weight reduction was found to decrease this risk [3-5]. Physical activity/exercise (PA/EX) was shown to be associated in a dose-dependent and inverse relationship with a 30 to 50 percent lower decrease of tumor risk in the most active individuals [6]. To further improve prevention strategies and therapeutic management in risk groups more clinical and epidemiological studies with quantitative data using highly sensitive risk biomarkers and their modification by lifestyle factors are urgently needed.

Disease, Oxidative DNA Damage Products and Risk Prediction Models

To quantify tumor risks (including CRC) a series of compounds 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 (ROS) produced in excess as a consequence of increased endogenous and exogenous oxidative stress [7,8]. Elevated levels of 8-oxo-dG have been found in many conditions and diseases with an increased cancer

risk including T2D [9-14]. In a recently published clinical cross-sectional study comparing urinary 8-oxo-dG in individuals with different CRC-risks we found that urinary excretion in patients with T2D (having a moderately elevated CRC risk) was in between those with curatively treated CRC (high risk for recurrence) and non-diabetic controls (average risk) [15]. Urinary excretion of 8-oxo-dG was significantly correlated with BMI (p=0.04) in all study participants, but not with the smoking status, age, alcohol consumption or gender. One clinically important application would be the implementation of stress biomarkers into predefined CRC-prediction models to further improve accuracy with inclusion into appropriate prevention programs. Thus, in a recently published meta-analysis compiling the data of two large scale population-based studies with >4000 individuals (ESTHER and Tromsö study) it was shown that the inclusion of reactive oxygen metabolites (ROM) assessed as total thiol (TTL) and hydrogen peroxide levels (d-ROM) into already existing models significantly improved their accuracy (C-statistics) [16]. Another study from the same group could show that CRC patients in the presence of elevated blood TTL and d-ROM levels had a poorer prognosis compared to those without these parameters [17]. Similar population-based trials with implementation of additional risk biomarkers such as urinary excretion levels of 8-oxo-dG into those prediction models presently are not available but are likely to further improve our prevention programs particularly in patients at an increased CRC-risk.

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 widely available and not entirely consistent. The great majority of clinical and experimental intervention studies in healthy volunteers as well as in patients belonging to risk groups such as 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 moderate intensity of EX, whereas at higher intensity levels oxidative DNA damage increased suggesting a U-shaped (hormesis) relationship. [18-25]. One possible explanation for this effect may be that cellular and humoral compensatory mechanisms such as exercise-induced activation of antioxidant defenses (e.g., superoxide dismutase, DNA repair systems) would be exhausted at higher EX intensities with a shift to more prooxidant compounds [26-28]. In our recently published study [15] we found that urinary 8-oxo-dG excretion was independent of the individual level of PA in all 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 [19,20]. 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 [26,27] 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 [15]. Despite these limitations further biomarker-guided long-term prospective interventional trials with individually tailored exercise programs are urgently needed to improve patient management particularly in those at increased CRC-risk such as obesity and T2D with particular emphasis on moderate intensity protocols to obtain optimal individual benefit.

Body Mass Index and 8-oxo-dG

In contrast to PA/EX the relationship of BMI oxidative DNA damage seems to be less clear as there are studies reporting inverse (negative) as well as positive correlations [29-32]. In a longitudinal study investigating a cohort of 179 healthy office workers Mizoue et al. found a negative correlation up to BMI 27 kg/m^2 [31], in morbidly obese patients undergoing bariatric surgery, however, a positive correlation was observed with a highly significant decrease 6 months after surgery [32]. Based on these data the authors of both groups suggested that there may possibly be a similar relationship of BMI with urinary 8-oxo-dG excretion as seen for PA/EX.; a negative correlation being observed at low/normal BMI (<27 kg/m^2) turning positive above this value [31,32]. When the participants in our recently published study (T2D, CRC, non-diabetic controls) were analyzed separately according to their diagnosis the observed positive correlation (p=0.04) was no longer significant. Additional BMI-models with multiple adjustments for the cofactors gender, age, BMI, alcohol consumption and smoking status yielded similar results (no correlation) [15]. In line with this data are results of our earlier study showing no significant correlation of BMI with urinary 8-oxodG excretion in CRC-patients [21]. It is, therefore, important to adjust for multiple confounding factors, when correlations of BMI with 8-oxo-dG in clinical and/or epidemilogical studies are investigated. Despite these limitations oxidative DNA damage biomarkers should be included into weight reduction programs particularly for the obese/morbidly obese individuals and those in whom bariatric surgery is planned [32]. Our finding of a positive correlation of BMI with urinary 8-oxo-dG excretion (in the non-diabetic controls) may further support the view that long-term (beneficial) effects of PA (or energy expenditure during EX) on risk biomarkers may be mediated at least partially by the weight loss (BMI reduction) as observed during appropriate exercise programs.

References

1. Ling S, Brown K, Miksza JK, Howells L, Morrison A, et al. (2020) Association of type 2 diabetes with cancer: A meta-analysis with bias analysis of unmeasured confounding in 151 cohorts comprising 32 million people. Diabetes Care 43(9): 2313-2322.

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2. Yuan C, Zhang X, Babic A, Morales-Oyarverde V, Zhang Y, et al. (2021) Preexisting type 2 diabetes and survival among patietns with colorectal cancer. Cancer Epidemiol Biomarkers & Prevention 30(4): 757-764.

3. Aleksandrova K, Nimptsch K, Pischon T (2013) Obesity and colorectal cancer. Frontiers in Bioscience. Elite 5(1): 61-77

4. Soltani S, Abdollahi S, Aune D, Ahmad J (2021) Body mass index and cancer risk in patients with type 2 diabetes: a dose-response meta-analysis of cohort studies. Scientific Reports 11: 2479.

5. Goodarzi G, Mozzaffari H, Raeisi T, Mehravar F, Ghazi ML, et al.(2022) Metabolic phenotypes and risk of colorectal cancer:systematic review and meta-analysis of cohort studies. BMC Cancer 22: 89.

6. Wang J, Huang L, Gao Y, Yanhong W, Shanquan C, et al. (2020) Physically active individuals have a 23% lower risk of any colorectal neoplasia and a 27% lower risk of advanced colorectal neoplasia than their non-active counterparts: Systematic review and meta-analysis of observational studies. Br J Sports Med 54(10): 582-591.

7. Roszkowski K, Jozwicki W, Blaszczyk P, Mucha-Maleck A, Siomek A (2011) Oxidative damage DNA: 8-oxoGua and 8-oxodG as molecular markers of cancer. Med Sci Monit 17(6): CR329-33.

8. Wu C, Chen ST, Peng KH, Cheng TJ, Wu KY (2016) Concurrent quantification of multiple biomarkers indicative of oxidative stress status using liquid chromatography-tandem mass spectrometry. Anal Biochem 512: 26-35.

9. Tamae K, Kawai K, Yamasaki S, Kawanami K, Ikeda M, et al. (2009) Effect of age, smoking and other lifestyle factors on urinary 7-methylguanine and 8-hydroxydeoxyguanosine. Cancer Sci 100(4): 715-721.

10. Lodovici M, Caldini S, Luceri C, Bambi F, Boddi V, et al (2005) Active and passive smoking and lifestyle determinants of 8-oxo-7,8-dihydro-2'-deoxyguanosine levels in human leukocyte DNA. Cancer Epidemiol Biomarkers Prev 14(12): 2975-2977.

11. Shin CS, Moon BS, Park KS, Kim SY, Park SJ, et al. (2001) Serum 8-hydroxy-guanine levels are increased in diabetic patients. Diabetes Care 24(4): 733-737.

12. Li YS, Song MF, Kasai H, Kasai K (2013) 8-hydroxyguanine in urine and serum as an oxidative stress marker: effects of diabetes and aging. JUOEH 35(2): 119-127.

13. Waris S, Winklhofer-Roob BM, Roob JM, Fuchs S, Sourij H, et al. (2015) Increased DNA dicarbonyl glycation and oxidation markers in patients with type 2 diabetes and link to diabetic nephropathy. J Diabetes Res pp. 915486.

14. Broedbaek K, Siersma V, Henriksen T, Weimann A, Petersen M, et al. (2015) Urinary markers of nucleic acid oxidation and cancer in type 2 diabetes. Redox Bio 4: 34-39.

15. Allgayer H, Owen R, Wiskemann J, Bussas U, Ulrich CM, et al. (2021) Tumor risk biomarkers and physical activity in type 2 diabetes, patients with colorectal cancer and individuals without diabetes. Endocrine Metabolic Science 3: 100091.

16. Gao X, Wilsgaard T, Jansen EH, Holleczek B, Zhang Y, et al. (2019) Prediagnostic derivatives of reactive oxygen metabolites and the occurrence of lung, colorectal, breast and prostate cancer: An individual participant data meta-analysis of two large populatio-based studies. Int J Cancer 145(1): 49-57.

17. Boakye D, Jansen L, Schöttker B, Jansen EHJM, Schneider M, et al. (2020) Blood markers of oxidative stress are associated with poorer prognosis in colorectal cancer patients. Cancer Epidemiol 147(9): 2373-2386.

18. De Lemos ET, Oliveira J, Pinheiro JP, Reis F (2012) Regular physical exercise as a strategy to improve antioxidant and anti-inflammatory status: benefits in type 2 diabetes mellitus. Oxid Med Cell Longev 741545.

19. Nojima H, Watanabe H, Yamane K, Kitahara Y, Sekikawa K, et al. (2008) Effect of aerobic exercise training on oxidative stress in patients with type 2 diabetes mellitus. Metabolism 57(2): 170-176.

20. Dimauro I, Sgura A, Pittaluga M, Magi F, Fantini C, et al. (2017) Regular exercise participation improves genomic stability in diabetic patients: an exploratory study to analyse telomere length and DNA damage. Sci Rep 7.

21. Allgayer H, Owen RW, Nair J, Spiegelhalter B, Streit J, et al. (2008) Short-term moderate exercise programs reduce oxidative DNA damage as determined by high-performance liquid chromatography-electrospray ionization-mass spectrometry in patients with colorectal carcinoma following primary treatment. Scand J Gastroenterol 43(8): 971-978.

22. Pittaluga M, Sgadari A, Tavazzi B, Fantini C, Sabatini S, et al. (2013) Exercise-induced oxidative stress in elderly subjects: the effect of red orange supplementation on the biochemical and cellular response to a single bout of intense physical activity. Free Radic Res 47(3): 202-211

23. Cash SW, Beresford SA, Vaughan TL, Heagerty PJ, Bernstein L, et al. (2014) Recent physical activity in relation to DNA damage and repair using the comet assay. J Phys Act Health 11(4): 770-776.

24. Sallam N, Laher J (2016) Exercise modulates oxidative stress and inflammation in aging and caradiovascular disease. Oxdative Med Cell Longev 2016: 7239639.

25. Radak Z, Ishihara K, Tekus E, Varga C, Posa A, et al. (2017) Exercise, oxidants and antioxidants change the shape of the bell-shaped hormesis curve. Redox Biol 12: 285-290.

26. Berzosa C, Cebrian I, Fuentes-Broto L, Gomez-Trullen E, Piedrafita E, et al. (2011) Acute exercise increases plasma total antioxidant status and antioxidant enzyme activities in untrained men. J Biomed Biotechnol 2011: 540458.

27. Diaz KM, Feairheller DL, Sturgeon KM, Williamson ST, Brown MD (2011) Oxidative Stress Response to Short Duration Bout of Submaximal Aerobic Exercise in Healthy Young Adults. Int J Exerc Sci 4(4): 247-256.

28. Chen SK, Hsieh WA, Tsai MH, Chen CC, Hing AI, et al. (2003) Age-associated decrease of oxidative repair enzymes, human 8-oxoguanine DNA glycosylase (hOggI) in human aging J Rad Res 44(1): 31-35.

29. Al-Aubaidy HA, Jelinek HF (2011) Oxidative DNA damage and type 2 diabetes melitus. Eur J Endocrinol 164: 899-904.

30. Irie M, Tamae K, Iwamoto-Tanaka N, Kasai H (2005) Occupational and lifestyle factors and urinary 8-hydroxyguanosine. Cancer Sci 96(9): 600-606.

31. Mizoue T, Tokunaga S, Kasai H, Kawei K, Sato M, et al. (2007) Body mass index and oxidative DNA damage: a longitudinal study. Cancer Sci 98(8): 1254-1258.

32. Kocael A, Erman H, Zengin K, Kocael PCA, Kormaz GG, et al. (2014) The effects on oxidative DNA damage of laparascopic band application in morbidly obese patients. Can J Surg 57(3): 183-187.

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