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Interventions targeted at oxidatively generated modifications of nucleic acids focused on urine and plasma markers

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ABSTRACT

Oxidative stress is associated with the development and progression of numerous diseases. However, targeting oxidative stress has not been established in the clinical management of any disease. Several methods and markers are available to measure oxidative stress, including direct measurement of free radicals, antioxidants, redox balance, and oxidative modifications of cellular macromolecules. Oxidatively generated nucleic acid modifications have attracted much interest due to the pre-mutagenic oxidative modification of DNA into 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG), associated with cancer development. During the last decade, the perception of RNA has changed from that of a 'silent messenger' to an 'active contributor', and, parallelly oxidatively generated RNA modifications measured as 8-oxo-7,8-dihydro-guanosine (8-oxoGuo), has been demonstrated as a prognostic factor for all-caused and cardiovascular related mortality in patients with type 2 diabetes. Several attempts have been made to modify the amount of oxidative nucleic acid modifications. Thus, this review aims to introduce researchers to the measurement of oxidatively generated nucleic acid modifications as well as critically review previous attempts and provide future directions for targeting oxidatively generated nucleic acid modifications.

1. Introduction

The concept of 'oxidative stress' was introduced more than 30 years ago to describe an imbalance between pro-oxidants and antioxidants in favor of pro-oxidants [1]. This indicated a concept used in relation to pathophysiological processes. Increasing knowledge of reduction-oxidation (redox) signaling and redox control, which is essential for cellular homeostasis, has resulted in the concept becoming non-specific and, therefore, being misused [2]. Attempts have been made to redefine the usage of this concept from describing a global view of the organism to a specific redox imbalance [3]. Differentiation of oxidative stress into 'oxidative distress' and 'oxidative eustress' depending on whether the redox process induces damaging modifications of molecules or involves essential regulatory processes, has also been suggested [4]. However, it is difficult to distinguish 'distress' and 'eustress'; as it appears to be a continuous transition.

2. Sources of oxidative stress

Reactive species are species that easily react with and modify various molecules; thus, promoting redox processes and oxidative stress. Reactive species are categorized depending on their chemical composition, as reactive oxygen species (ROS), reactive nitrogen species, reactive chlorine/bromine species, reactive sulfur species, reactive carbonyl species, and reactive selenium species. Each group is further sub-divided, depending on whether the molecule has an unpaired electron, i.e., free radicals and non-radicals [4]. Mitochondria generate superoxide as a by-product of the electron transport chain and are considered a major contributor to ROS generation [5]. In addition, various enzyme systems (e.g., NADPH oxidase, xanthine oxidase) can generate reactive species [4]. The cellular localization of reactive species production is very important as the majority of reactive species have a short half-life [6], and, thus, easily react with macromolecules at the site of generation. Data suggest the existence of compartmentalization of oxidative stress [7–11]. Thus, it is important to measure the markers of oxidative stress representative of the relevant cellular compartments.

In addition to the endogenous sources of reactive species, exogenous sources also contribute to the formation of reactive species. Several environmental factors such as pollutants, radiation, and ultraviolet light

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Abbreviations

8-oxodG	8-oxo-7,8-dihydro-2′-deoxyguanosine
8-oxoGuo	8-oxo-7,8-dihydroguanosine
8-oxoGua	8-oxo-7,8-dihydroguanine
ACEi	angiotensin-converting enzyme inhibitor
CAT	catalase
+ CI	confidence interval
Bach1	BTB and CNC homology 1
ECD	electrochemical detection
ELISA	enzyme-linked immunosorbent assay
FPG	formamidopyrimidine DNA glycosylase
GC	gas chromatography
GLP-1	glucagon like peptide 1
GSH	glutathione
GSSG	glutathione disulfide
GPx	glutathione peroxidase
GRx	glutathione reductase
LC	liquid chromatography
m/z	mass over charge ratio
MRM	multiple reaction monitoring
MS	mass spectrometry
RCT	randomized controlled trials
redox	reduction-oxidation
ROS	reactive oxygen species
RASi	renin-angiotensin system inhibitor
SGLT2i	sodium glucose cotransporter 2 inhibitor
SG	specific gravity
SOD	superoxide dismutase
T2D	type 2 diabetes
UHPLC	ultra-high-performance liquid chromatography
UPLC	ultra-performance liquid chromatography

result in generation of reactive species [12].

3. Measuring oxidative stress

Measuring oxidative stress *in vivo* presents a great challenge. It constitutes a major limitation and may be the most important reason why oxidative stress has not been established in the clinical management of any disease. Methods for measuring oxidative stress can be separated into four strategies each possessing advantages and disadvantages. I) *Measuring reactive species*. Direct measurement of reactive species is preferable; however, this approach possesses great difficulties *in vivo* due to the unstable structure and, hence, short half-lives of the reactive species [6,13]. Thus, it is an inappropriate method in human body fluids. II) *Measuring antioxidants*. The obvious challenge in measuring antioxidants *in vivo* is that the most important antioxidants, to a large extent, are found intracellularly [14]. Thus, interpretation of plasma concentrations should be made with caution. The information accessed, when measuring a combination of plasma antioxidants (e.g. total antioxidant capacity) is disputable, and, at the moment, only separate measurement of antioxidants can be encouraged [2]. III) *Measuring cellular redox balance*. The ratio of redox couples such as reduced and oxidized glutathione (i.e., GSH/GSSG) can be used to describe the cellular redox state. However, extracellular glutathione concentrations are many-fold lower than the cellular concentrations, they are not regenerated, and, thus, may not reflect the intracellular concentrations or redox state in the cell [15]. As with measuring antioxidants, caution is needed when interpreting concentrations from human fluids [16]. IV) *Measuring oxidatively generated modifications of macromolecules.* Oxidatively generated modifications of macromolecules are used as an indirect measurement of reactive species. They are considered a 'finger print,' i.e., high concentrations of oxidized macromolecules result from a high degree of oxidative stress [17].

Each of the strategies has numerous markers describing different components in redox signaling and redox control within several different cellular compartments. This complexity highlights the importance of precision in describing a measured reactive species, antioxidant, redox couple, or oxidized macromolecule and reserve generalizing terms such as 'oxidative stress' to situations with no specific measurement.

4. Oxidative stress in physiology and pathophysiology

Redox signaling and control in cellular physiology has attracted increasing attention during the past decades [18]. Details regarding essential redox processes are beyond the scope of this review, which will instead focus on pathophysiologic consequences associated with oxidative stress.

Oxidative stress is associated with the development and progression of numerous diseases including neurodegenerative- [19], cardiovascular- [20], metabolic- [21], psychiatric diseases [22], and cancer [23] as well as aging [24]. However, the impact of oxidative stress on different diseases is not well defined to a large extent, and a direct causality is not established. Thus, knowledge regarding oxidative stress in relation to disease development and progression is yet to be further explored. The best strategy is to identify an applicable intervention to decrease a specific relevant redox imbalance for a given disease and then evaluate the clinical impact of an improved specific redox imbalance in the given disease. In hindsight, this is probably where many studies lost focus and the reason why antioxidant therapy is not considered in clinical settings.

5. Antioxidants and their therapeutic potential

Antioxidants are substances that delay or prevent oxidative modifications of oxidizable substrates [25]. Given this definition, it is no surprise, that a myriad of different antioxidants has been described [6]; however, this concept should be avoided in clinical setting. Instead, the specific antioxidant or specific reactive species/redox couple affected, or oxidized macromolecules should be identified to distinguish clinically relevant antioxidative effects.

Antioxidants are traditionally grouped into enzymatic and non-enzymatic antioxidants. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) represent enzymatic antioxidants, which act as the first line antioxidant defense, with a direct effect of catalyzing reactions that convert superoxide ($O_2^{\cdot-}$) into the less reactive specie, hydrogen peroxide (H_2O_2) (catalyzed by SOD), which is then converted to water (catalyzed by CAT or GPx) [26]. Glutathione reductase (GRx) is an example of an indirect antioxidant enzyme, that converts glutathione disulfide (GSSG) to GSH [27]. The non-enzymatic antioxidants can be classified depending on origin, as endogenous (e.g., GSH, coenzyme Q10, uric acid, bilirubin, L-arginine) or exogenous non-enzymatic antioxidants (e.g., α-tocopherol, ascorbic acid, β-carotenoid, flavonoids, zinc) [27], with the latter being a major focus of antioxidant supplementary therapy.

Previously, observational studies have revealed that subjects with a dietary pattern or on vitamin supplementation rich in non-enzymatic antioxidants were at lower risk of cardiovascular disease [28–30]. This observation led to an investigation of the effect of antioxidant supplement (i.e., α-tocopherol, β carotene, and ascorbic acid) on cardiovascular diseases. The studies included a large number of participants and were well designed but had at least two major flaws; no biomarker associated with cancer development or progression was used to evaluate the treatment response of the antioxidant treatment and the target group was not defined or chosen with high oxidative stress values.

To a large extent, the studies outcomes were disappointing, showing no effects on cardiovascular disease or cancer developement [31–35]. However, one study demonstrated that α-tocopherol reduced major cardiovascular events (nonfatal myocardia infarcts and death of cardiovascular cause) in patients with coronary atherosclerosis; further analysis revealed that the effect was driven by a reduction of non-fatal myocardial infarcts but not death of cardiovascular cause [36]. Surprisingly, some of the studies raised the question of the potential harmful effects of antioxidant supplementation among subjects that smoked, as one study revealed a higher risk of fatal coronary heart disease following α-tocopherol and β-carotene treatment [33] and two studies showed increased risk of lung cancer following β-carotene treatment and a combination of β-carotene and retinol treatment, respectively [31,34]. These diverging effects indicate potentially different responses with respect to the life style habits of the participants (i.e., smoking status and dietary pattern [37]), which should be considered when planning an intervention trial. The mechanism that explain the association between lung cancer and β-carotene/retinol treatment is far from understood. However, recent experimental studies in animals and cell cultures suggest that antioxidants may inhibit the degradation of transcription factor BTB and CNC homology 1 (Bach1), and stabilization of Bach1 seem to promote metastasis of lung cancer cells [38,39].

The large randomized controlled trials (RCTs) were expensive, and given the overall disappointing outcome, no new RCTs on the same scale have been conducted to evaluate antioxidant therapy. Instead, the focus has been on developing a biomarker for disease progression and evaluating the effects of interventions on that biomarker as a surrogate for antioxidant effects.

Despite the lack of solid effects of antioxidant therapy on disease progression, progressive use of non-specific antioxidants in various diseases associated with increased levels of oxidative stress has been observed. This has generated a large industry and inflicted huge expenses on patients as well as healthy subjects without any documented benefits. Given the current evidence, careful evaluation of the beneficial effects of antioxidants as well as the potential adverse outcomes is necessary.

In an extreme outcome, a powerful antioxidant could quench all oxidative reactions – and, thereby, life; therefore, a delicate balance must be sought. At this moment, prevention by avoiding exposure to pro-oxidants must be considered the best antioxidant defense. Like the plankton that descends to avoid solar radiation [6], we can attempt to avoid cigarette smoke, pollution, radiation, and unhealthy life-styles, including overeating/obesity. Hopefully, this review will elucidate other potential interventions that may decrease oxidatively generated modifications of nucleic acids, in cases were prevention is not sufficient or is too late.

6. Oxidatively generated modifications of nucleic acids

Like lipids and peptides, nucleic acids are constantly oxidized within the cell. The rate and handling of oxidation differs between DNA and RNA [40]. DNA is double stranded and contains protective proteins, whereas RNA is single stranded and is not protected by proteins. The cellular location of RNA, close to the mitochondria, makes it more susceptible to oxidation [41]. Well known repair mechanisms are described for the products of DNA oxidation [42], which is in contrast to RNA oxidation where repair mechanisms have been suggested but degradation and elimination of oxidized RNA seems to be the predominant strategy [40]. From these distinct differences between RNA and DNA oxidation, the level of RNA oxidation obviously exceeds DNA oxidation [43].

The comet assay is a method used for determining DNA strand breaks within cells. Using a protocol involving incubation with endonuclease III and formamidopyrimidine DNA glycosylase (FPG), the enzymes generate a strand break when an oxidized base is detected. Thus, the amount of oxidized bases can be detected using this method [44]. The question of whether peripheral blood cells are surrogates for target organs has not been answered, and it may be naïve to consider peripheral blood cells as representatives of the many different target organs. The interpretation of results from cellular oxidized nucleosides is distinct different from measuring oxidized nucleosides in plasma and urine, since the oxidized cellular nucleosides characterizes the accumulation of oxidized nucleic acids, whereas oxidized nucleosides in human body fluids represent their formation [45]. Therefore, this review does not include detailed information regarding analysis methods or intervention studies measuring oxidatively generated modifications of nucleic acids in cells or tissue.

Several oxidation products of nucleic acids are described [46,47] but the low redox potential of guanine makes it the most susceptible to oxidation [41]. Thus, guanine is the most investigated base, and the oxidation products of its nucleosides; 8-oxo-7,8-dihydro-guanosine (8-oxodG) and 8-oxo-7,8-dihydroguanosine (8-oxoGuo) are the focus of the present review.

Given the different cellular locations of DNA and RNA, the markers represent different intracellular information. DNA is present in the nucleus and mitochondria [48,49], whereas RNA is predominantly found in the cytosol [40]. The contribution from the nucleotide pool to the generation of 8-oxodG and 8-oxoGuo is disputable. Guanine found in RNA has been estimated 75 times greater than guanine in the nucleotide pool [40]. Thus, it would require an extensive oxidation of the nucleotide pool if this is the primary source of 8-oxoGuo and 8-oxodG. However, propensity to oxidation may differ between the nucleotide pool and RNA/DNA. Even though, the mechanism responsible for excretion of oxidized guanine in RNA/DNA is undefined, the process has been shown to occur [50]. Thus, we consider guanine found in RNA/DNA as the most plausible source of 8-oxoGuo/8-oxodG, due to the considerable quantitative differences in guanine distribution. However, no quantitative data exist to support either view. As a result of the different cellular location of DNA and RNA, the sources that generate reactive species responsible for the oxidation of DNA and RNA are likely to differ, and, thus, DNA and RNA oxidation may reflect different causes of redox imbalance.

Both the causes and the consequences of DNA and RNA oxidation are different. Historically, DNA oxidation has attracted predominant focus due to the pre-mutagenic potential of the G-C to T-A transversion mutation that 8-oxodG may cause [51], as well as the potential linkage with aging through e.g., telomere shortening and cell senescence [52]. Several carcinogenic substances (e.g., tobacco smoke, exposure to asbestos, and environmental pollution) are known to increase DNA oxidation [48]. However, a convincing association between DNA oxidation and many carcinogenic diseases is still not well established. Some examples of associations between carcinogenic diseases and increased DNA oxidation, measured by 8-oxodG, are found among patients with breast cancer, whereas two studies found elevated urinary excretion rates of 8-oxodG among patients with breast cancer compared to those matched controls (one of the studies found elevated excretion rates only among estrogen receptor positive patients) [53,54]. Another nested case-control study revealed elevated urinary excretion rates of 8-oxodG among patients with lung cancer who never smoked, which was not evident among patients with lung cancer who smoked [55]. Two studies demonstrated higher 8-oxodG excretion rates among patients with colorectal cancer [56,57]. Another study revealed higher urinary excretion of 8-oxodG rates among children with acute leukemia compared to matched controls using ELISA [58]. These studies indicate some association between the urinary excretion of 8-oxodG and carcinogenesis, but data were generated from (nested) case-control studies. Notably, the measurement of plasma/urine 8-oxodG may not include the non-excreted 8-oxodG that causes the G-C to T-A transversion accumulation within the cell.

In addition to carcinogenesis, increased urinary excretion rates of 8-oxodG are found among patients with schizophrenia [59] and bipolar disorder [60]. Furthermore, a study with a smaller sample size revealed

increased 8-oxodG excretion rates adjusted to creatinine excretion in patients with chronic kidney disease compared to healthy controls [61]. However, this association might be explained by lower urinary excretion rates of creatinine among patients with chronic kidney disease and, thus, higher 8-oxodG/creatinine ratios [62]. Patients with several neurodegenerative diseases also present higher levels of 8-oxodG compared to controls. In patients with Parkinson's disease and multiple system atrophy, higher 8-oxodG/dG ratios were found in the serum using an ELISA method [63], whereas patients with Alzheimer's disease present higher concentrations in several brain regions [64]. Thus, increased excretion rates and concentrations of 8-oxodG seem to be associated with a number of diseases; however, further investigations are necessary to elucidate this association and to investigate potential causality.

To a large extent, the consequences of RNA oxidation differ from those of DNA oxidation. One of the distinguished differences is that RNA oxidation does not seem to be associated with cancer development [65]. Furthermore, a striking finding is that RNA oxidation, measured by urinary excretion of 8-oxoGuo, is associated with all-cause mortality in patients with type 2 diabetes (T2D). This was found both among treatment-naïve [7] as well as treatment-engaged patients with T2D [8,9]. Furthermore, an association between 8-oxoGuo excretion rates and mortality of cardiovascular causes was found in patients with T2D [9,66]. None of these associations were evident with DNA oxidation as measured by 8-oxodG urinary excretion rates [7–9]. The association between T2D and oxidative stress has been known and discussed for several years. However, a causality with development or progression has not been established [21]. Thus, the association between RNA oxidation and increased risk of death is a novel finding, but whether RNA oxidation is part of the pathogenesis or a result thereof is yet to be explored. Furthermore, one observational study found that reducing the urinary excretion rate of 8-oxoGuo in a manner that a patient changes from highest quartile of RNA oxidation to the lowest quartile of RNA oxidation compared to those that remained in the highest quartile of RNA oxidation presented an all-cause mortality hazard ratio (HR) of 0.31 (95% confidence interval: 0.14–0.68) [8]. This indicates a considerable therapeutic potential and motivates us and hopefully others to explore potential interventions that may modify RNA oxidation in this patient group.

Additionally, increased urinary 8-oxoGuo excretion rates are found in patients with hereditary hemochromatosis [11], chronic obstructive pulmonary disease (COPD) [67], and psychiatric disorders [59,60]. RNA oxidation may also be involved in the development of neurodegenerative diseases [68].

The cellular consequences of RNA oxidation seem to involve disturbances in both protein synthesis (i.e., translational stunning, mutated- or truncated proteins) [69] and cellular signaling [70]. These cellular disturbances could explain the association with RNA oxidation and disease progression, which differentiate the marker from DNA oxidation. As mentioned previously, the sources of reactive species causing oxidation may very well differentiate between nucleic acids, whereas mitochondria must be assumed as the predominant source of reactive species oxidizing RNA. Thus, it could be argued that RNA oxidation may present a marker of mitochondrial dysfunction more than a direct pathophysiological element. If so, interventions should be aimed at modifying mitochondrial function.

We recognize both 8-oxodG and 8-oxoGuo as valuable markers of intracellular oxidative stress. Each marker presents different information regarding oxidative stress and provides a different clinical relevance. However, both markers are unable to distinguish between organ of origin when measured in human body fluids. Thus, changes in these markers following disease or intervention may only be detectable if the change is systemic and not restricted to a single organ. Hopefully, future technical progress will enable the measurement of organ specific 8-oxodG and 8-oxoGuo. At the moment, the major reason for the diminished clinical relevance of these markers is the lack of consistency between their analysis results using different analysis methods.

7. Collection of sample material

Oxidized nucleosides are formed within the cell. The oxidized nucleosides can be repaired (if derived from DNA), accumulated, or excreted from the cell. The cellular excretion process is still not well characterized. However, when the oxidized nucleoside is injected into the bloodstream, it will be transferred to the kidney and excreted in urine [71]. Oxidized nucleosides can be measured in tissue (cells), plasma/serum, and urine. The interpretation of the results should be clearly distinguished depending on the analyzed material. It is reasonable to assume that the kidneys will filter oxidized nucleosides without reabsorption, given the small water-soluble structure of the molecule. Thus, plasma/serum concentrations are difficult to interpret and may reflect kidney function more than the degree of oxidative stress [40].

Urinary excretion rates of oxidized nucleic acids determine the newly formed oxidized nucleosides [72]. Some researchers still report urine concentrations per unit volume, without adjustments for urinary flow. This is conceptually wrong and should not be used, as the hydration state will determine the level of oxidized nucleosides.

In general, three different strategies can be used to measure the total amount of excreted oxidized nucleosides: *1) Collection of 24-h urine* with determination of urine volume to calculate the nanomoles excreted throughout a 24-h period. If compliance to urine collection is correct, this is considered the standard reference method. However, our clinical experience tells us that a strict protocol is needed to ensure adequate compliance e.g., text message reminders and evaluation of compliance [73]. *2) Creatinine adjusted results.* In many studies, it is not feasible to collect 24-h urine and, thus, a spot urine sample is collected. Creatinine adjustment is the most used method to correct for urinary flow. This method is widely used in the clinic as well (e.g., to determine albuminuria); however, in an intervention study, care is needed so that the intervention does not affect creatinine excretion and, thus, cause changes in the 8-oxo-nucleoside/creatinine ratio. In studies exploring interventions that cause changes in weight or muscle mass [74,75] and protein intake [76], it is not appropriate to use 8-oxo-nucleoside/creatinine ratios, nor should the participant have performed intense exercise before the urine collection [77]. *3) Density adjusted results.* In cases where a spot urine collection is available, but urine creatinine may provide a confounded estimate of the hydration state, density adjustment using specific gravity (SG) can be used [78]. In studies with children, SG adjustment may even be superior to creatinine adjustment for determining the hydration state [79].

It is important to obtain comparable results between studies; thus, we prefer that different study groups use the same method to correct for the hydration state (e.g. 8-oxo-nucleoside/creatinine). The urine creatinine correction has it potential flaws, and a modified method including age, gender, sex, and ethnicity may be preferable if a consensus could be established [80].

8. Methods for measuring oxidatively generated modifications of nucleic acids

Various methods are available to measure the concentration of a given molecule. These methods are based on different characteristics of the molecule, such as the absorption or emission of light. Urine contains many potential interfering substances and, thus, measuring light absorption is inappropriate. Other relevant techniques detect substances through their mass, electrical current, or immunohistochemical reaction. This results in four different approaches that have been used to determine oxidized nucleosides in human body fluids: liquid chromatography (LC) coupled with either 1) mass spectrometry (MS) or 2) electrochemical detection (ECD), 3) gas chromatography (GC) coupled with MS, and 4) enzyme-linked immunosorbent assays (ELISA).

The primary analytical challenge when determining oxidized nucleosides is achieving high specificity. Several efforts have resulted in progress to improve the methods used and increase researchers awareness regarding this analytical issue [81], but this still needs to be fully implemented. Additionally, the importance of the pre-analytical handling should also be considered [82].

8.1. LC-MS

The separation method that is usually applied is reverse-phase LC, wherein a liquid sample is added to a column, and through the column, substances are separated depending on polarity using a nonpolar stationary phase and a polar mobile phase. Thus, the nonpolar material is retained longest [83]. After LC separation, detection is performed by MS. A mass spectrometer contains three elements: 1) an ion source, 2) a mass analyzer, and 3) a detector. The ion source ionizes substances. Then, the mass analyzer separates ions based on the desired mass over charge ratio (m/z), and detection occurs by generation of electricity currents from the ions [84].

The LC-MS/MS method is considered a highly specific method, especially when a qualifier ion multiple reaction monitoring (MRM) pair is used together with a quantifier ion MRM pair [85]. It is further necessary to use an isotope dilution technique to account for variability within the analysis. A major strength of the method is the availability of stable isotope labelled internal standards. The specificity of LC-MS/MS is increased by using ultra-performance liquid chromatography (UPLC)/ultra-high-performance liquid chromatography (UHPLC). The major disadvantage with LC-MS/MS is the price of the equipment and the high level of expertise needed to operate the instrument [86].

8.2. LC-ECD

Instead of coupling LC with MS, LC can also be coupled with ECD. ECD detects electric fields based on oxidation or reduction processes [87]. The method is considered as a less specific detection method compared to MS/MS [88]. Thus, the quality of the LC separation is essential [86]. Due to the technical development of LC-MS/MS during the last few years, LC-ECD is currently almost completely abandoned.

8.3. GC-MS

The GC method is based on vaporization of the sample before separation through the column [89]. GC-MS is considered a very specific method. However, the sample pre-purification and preparation processes are rather time consuming. Previously, the risk of autooxidation during sample preparation (nucleoside extraction, hydrolysis, and derivatization) has been a substantial challenge using this method, especially when analyzing tissue samples. Urine samples do not pose the same risk of autooxidation due to a higher ratio between oxidized nucleosides and non-oxidized nucleosides; however, solid phase extraction is still necessary to allow derivatization [86]. Thus, this method is mostly abandoned.

8.4. ELISA

ELISA is based on an immunological reaction, where primary antibodies bind to oxidized nucleosides, then secondary enzyme-labelled antibodies bind to the primary antibody to allow detection [90]. This method is often used to determine 8-oxodG due to its low cost and easy laboratory analyses. Several ELISA kits exist using different antibodies. Thus, we cannot exclude that the quality between the kits may vary. The major issue when using ELISA is low specificity. Thus, much higher values are measured using ELISA methods [88]. The unreliable results using ELISA for detection of oxidized nucleoside are illustrated in a recent meta-analysis, where no difference in 8-oxodG excretion was found when smokers were compared with non-smokers using the ELISA methods. However, using chromatography methods showed a significant difference (mean(95% confidence interval(CI)): 29.3 (17.3; 41.3) %) between smokers and non-smokers [91]. Efforts have been made to improve the agreement between ELISA and LC-MS/MS, including identifying interfering compounds [92,93]. However, presently the specificity of the ELISA methods is so low that its usage cannot be recommended.

8.5. Comparison of analytical methods

This review focused on intervention studies conducted in humans that measured 8-oxodG or 8-oxoGuo. We identified the appropriate studies based on three criteria (and their synonyms): 1) measurement of 8-oxodG and 8-oxoGuo, 2) intervention studies, and 3) conducted in

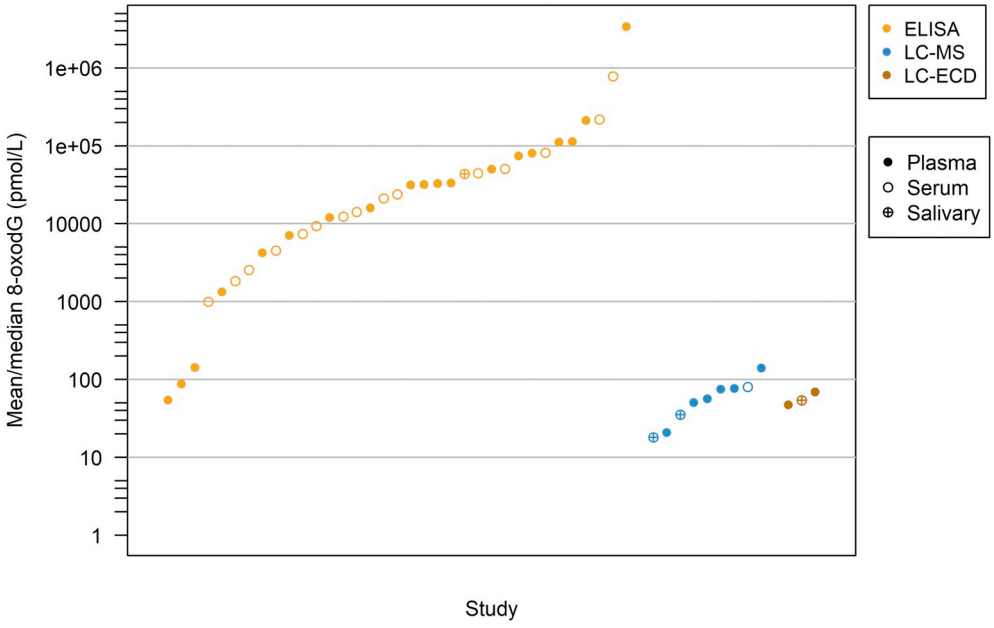

Fig. 1. Plasma, serum, and salivary concentrations of 8-oxodG. Fig. 1 illustrates the mean/median plasma, serum, and salivary concentration of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) measured by enzyme-linked immunosorbent assays (ELISA), liquid chromatography electrochemical detection (LC-ECD), or liquid chromatography tandem mass spectrometry (LC-MS/MS), reported by the following studies [94–128] The studies reporting plasma values of LC-MS/MS and LC-ECD are not intervention studies but used as references since none of the identified intervention studies used these methods. The x-axis presents each study sorted by 8-oxodG concentration rank ordered and separated by the analysis method. The y-axis is logarithm transformed.

humans. We identified 6613 studies (26th Februrary 2019) using the following search in PubMed: '(((((((((oxidative nucleic acid modifications) OR oxidative nucleic acid damage) OR nucleic acid modifications by oxidation)) OR (((((((((8-oxodG) OR 8-OHdG) OR dna oxidation) OR oxidative dna modifications) OR oxidative dna damage) OR 8-oxo-7,8-dihydro-2'-deoxyguanosine)))) OR (((((((8-oxoGuo) OR 8-OHGuo) OR rna oxidation) OR oxidative dna modifications) OR oxidative rna damage) OR 8-oxo-7,8-dihydroguanosine) OR 8-oxo-7,8-dihydro-guanosine))) AND (((rct) OR randomised controlled trial) OR intervention)) AND ((((human) OR patient) OR subject) OR individual'. From the title and abstract of the 6613 identified studies, a total of 232 were selected for full reading. Thirty-five studies [94–128] were identified as having measured 8-oxodG in plasma and 78 studies [11,104,129–204] were identified as having measured 8-oxodG/creatinine in urine; these were selected for comparing the concentrations between analysis procedures. None of the studies used LC-ECD and LC-MS/MS methods for determining 8-oxodG in plasma; thus, we used non-intervention studies as references for the LC-ECD [82,205] and LC-MS/MS methods [206–210].

Fig. 1 and Fig. 2 are graphical illustrations of the mean/median concentration from the identified studies measured using different methods (i.e., ELISA, LC-ECD, and LC-MS) in plasma/serum/saliva and urine (spot samples), respectively. We did not discriminate between plasma, serum, and saliva since the concentrations seemed similar. Furthermore, we did not distinguish between ELISA kits, since the information in many manuscripts was inadequate. LC-ECD and LC-MS seemed to consistently detect plasma/serum/saliva concentrations below 100 pmol/L, whereas ELISA detected concentrations up to 10,000-fold higher; in some cases, there seemed to be confusion about the units reported. One study is omitted in Fig. 2 due to a very high reported urinary excretion of 8-oxodG [184]. We assume that they have presented a wrong unit.

The concentration of 8-oxodG in urine samples seems to vary less compared to that in plasma samples using the ELISA method. The 8-oxodG concentrations reported with ELISA are approximately 2-fold higher than those with the LC-MS (median: 4.84 vs 2.25 nmol/mmol creatinine), and the majority of ELISA kits cannot distinguish between the RNA and DNA nucleoside forms [211,212] and may also cross-react with urea [211]. This severely restricts the usage and interpretation of results using the ELISA method.

9. Interventions that target oxidatively generated modifications of nucleic acids

Reducing the rate of oxidatively generated modifications of both DNA and RNA may be clinically relevant given their associations with disease development and progression. To elucidate the clinical potential, an applicable intervention must first be identified, and the clinical impact should then be evaluated in a long-term setting; the former seems difficult, whereas the latter is costly. This review will discuss previously reported findings in this context. However, the majority of studies have to be interpreted with caution given that most studies used an ELISA method, which is problematic, especially in plasma samples (Fig. 1).

We used the same literature search strategy as described in '8.5 *Comparison of analytical methods*' and selected studies depending on the relevance of the intervention for the following sections.

9.1. Antioxidant therapy

The effect of α-tocopherol on 8-oxodG has been extensively studied both in combination with other antioxidant therapies [153,168,213–216], and as single administration [153,215,217,218]. All studies except one, found no effect of α-tocopherol on 8-oxodG [153,168,213–216,218]. The one study that found an effect of α-tocopherol on 8-oxodG measured urinary excretion rates, and investigated children with Down syndrome [217]. Children with Down syndrome express high levels of 8-oxodG [219], which might explain the different response to α-tocopherol treatment. However, the study reported urinary concentration values without correcting for urinary flow. The authors state that it may not be appropriate to correct for urinary flow using urine creatinine in children with Down syndrome. However, a different strategy should have been used (i.e., 24-h volume or density correction). Thus, differences in the hydration state of the participants could greatly impact the results and may explain why this was the only study that found an effect of α-tocopherol on 8-oxodG [217]. Ascorbic acid and β-carotene have also been investigated both in combination with α-tocopherol and other antioxidant therapies as well as single administration demonstrating no effect on 8-oxodG [153,168,171,213–216]. One study examined the effect of 1-h intravenous infusion of ascorbic acid (225 mg) and found that it prevented an ischemia-induced increase in 8-oxodG, evident during placebo treatment. However, the study used an ELISA method for

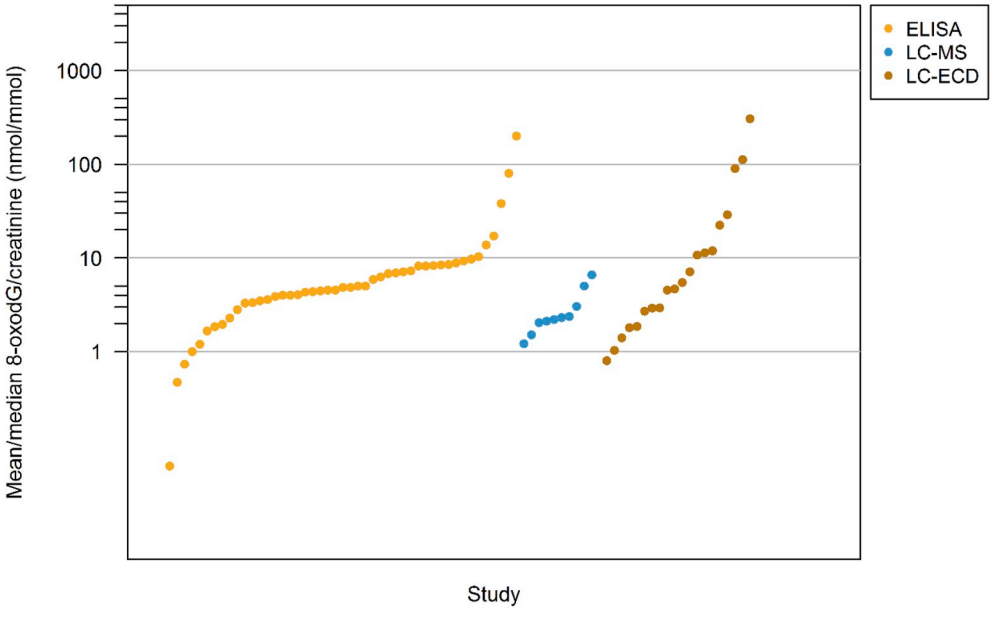

Fig. 2. Urinary excretion of 8-oxodG/creatinine. Fig. 2 illustrates the mean/median urinary excretion of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) measured by enzyme-linked immunosorbent assays (ELISA), liquid chromatography electrochemical detection (LC-ECD), or liquid chromatography tandem mass spectrometry (LC-MS/MS) as reported by the following studies [11,104,129–204]. The x-axis presents each study sorted by 8-oxodG concentration rank ordered and separated by the analysis method. The y-axis is logarithm transformed.

Table 1
Antioxidant therapy.

Intervention	Study design	Blinding	Total no. of subjects	Study duration (weeks)	Subject characteristics	Marker	Human fluid	Analysis methods	Results	Reference
1) α-tocopherol (400 IU/d), 2) α-lipoic acid (100 mg/d), 3) placebo	RCT	Single blinded	93	17	Children with Down syndrome	8-oxodG	Urine[a]	ELISA	α-tocopherol treatment decreased 8-oxodG compared to placebo. α-lipoic acid did not decrease 8-oxodG compared to placebo, however a reduction was observed within the treated group	[217]
1) α-tocopherol (300 mg/d) + ascorbic acid (400 mg/d), 2) placebo	RCT	Double blinded	256	52	Mild cognitive impairment	8-oxodG	Serum	ELISA	No difference in 8-oxodG between groups. However, significant reduction in 8-oxodG within both groups	[213]
1) Active capsules 1/d (folate (420 μg), ascorbic acid (234 mg), α-tocopherol (32 mg), β-carotene (7.5 mg), bioflavonoider (160 mg)), 2) placebo	RCT	Double blinded	60	4	Healthy subjects	8-oxodG	Urine	ELISA	No difference in 8-oxodG between groups. However, significant in 8-oxodG reduction within both groups	[214]
1) Placebo, 2) Vitamin suppl. (β-carotene (20,000 IU/d), α-tocopherol (400 IU/d), ascorbic acid (500 mg/d), selenium (100 μg/d), zinc (30 mg/d)). Both groups + high altitude exposure.	RCT	Double blinded	18	5	Healthy subjects	8-oxodG	Urine	HPLC-ECD	No difference in 8-oxodG between groups	[168]
1) α-tocopherol (182 mg/d), 2) ascorbic acid (500 mg/d), 3) α-tocopherol (182 mg/d)+ascorbic acid (500 mg/d), 4) placebo	RCT	Double blinded	48	52	Hypercholest-erolemia	8-oxodG	Urine	HPLC-ECD	No difference in 8-oxodG between groups	[215]
1) Placebo, 2) ascorbic acid (500 mg/d), 3) α-tocopherol (400 IU/d), 4) ascorbic acid (500 mg/d) + α-tocopherol (400 IU/d)	RCT	Double blinded	184	8	Healthy subjects	8-oxodG	Urine	ELISA	No difference in 8-oxodG between groups	[153]
High altitude winter training + 1) Vitamin suppl. (β-carotene (12 mg/d), α-tocopherol (400IU/d), ascorbic acid (500 mg/d), selenium (100 μg/d), zinc (30 mg/d)), 2) placebo	RCT	Single blinded	30	2	US Marine Corps volunteers	8-oxodG	Urine[a]	ELISA	No difference in 8-oxodG between groups	[216]
1) α-tocopherol (200 mg/d) + slow release ascorbic acid (500 mg/d) 2) α-tocopherol (200 mg/d), 3) ascorbic acid (500 mg/d), 4) slow-release ascorbic acid (500 mg/d), 5) coenzyme Q10 (oil) (90 mg/d), 6) coenzyme Q10 (granulate) (90 mg/d), 7) placebo	RCT	Single blinded	116	8	Healthy smoking subjects	8-oxodG	Urine	HPLC-ECD	No difference in 8-oxodG between groups	[218]
Ischemia (occluded artery flow for 5 min) follwing: 1) 1 h infusion of placebo (250 NaCl 0.9 g/l) or 2) ascorbic acid (1 g in 250 ml of NaCl 0.9 g/L solution)	RCT (cross-over)	Double blinded	18	1 day	Metabolic syndrome	8-oxodG	Serum	ELISA	3 and 9 min following artery occlusion serum 8-oxodg concentrations were significant higher in placebo group compared to ascorbic acid treated group	[107]
1) Ascorbic acid (750 mg/d), 2) Ascorbic acid (7500 mg/d)	RCT (cross-over)	Open label	6	6 days	Healthy subjects	8-oxodG[b]	Urine	HPLC-ECD	No statistically test described. Decline in absolute values of 8-oxodG following low dose treatment, but not following high dose treatment	[272]
1) β-carotene (20 mg/d), 2) placebo	RCT	Double blinded	163	14	Healthy smoking subjects	8-oxodG	Urine	HPLC-ECD	No difference in 8-oxodG between groups	[171]
1) Placebo, 2) selenium yeast (200 μg/d), 3) selenium yeast (285 μg/d), selenomethionine (200 μg/d)	RCT	Double blinded	69	39	Healthy subjects	8-oxodG	Urine	ELISA	Selenium (285 μg/d) treatment decreased 8-oxodG within the treated group.	[221]

(*continued on next page*)

Table 1 (*continued*)

Intervention	Study design	Blinding	Total no. of subjects	Study duration (weeks)	Subject characteristics	Marker	Human fluid	Analysis methods	Results	Reference
1) selenium (100 μg/d), 2) placebo	RCT	Not specified whether single or double blinded	103	13	Healthy subjects exposed to Hg (10–50 ng/ml in plasma)	8-oxodG	Urine[a]	HPLC-ECD	Selenium treatment significantly decreased 8-oxodG compared to placebo treatment.	[222]
1) Placebo (healthy BRCA carriers) 2) selenium (300 μg/d) (healthy BRCA carriers), 3) Placebo, (patients with breast or ovarian cancer, 4) selenium (300 μg/d) (patients with breast or ovarian cancer)	RCT	Double blinded	190	No information	Healthy BRCA carriers or patients with breast or ovarian cancer	8-oxodG	Urine	GC-MS (HPLC purified)	No difference in 8-oxodG between selenium and placebo treatment (among same study population)	[220]
1) Placebo, 2) α-lipoic acid (300 mg/d), 3) α-lipoic acid (600 mg/d), 4 α-lipoic acid (900 mg/d), 5) α-lipoic acid (1200 mg/d)	RCT	Double blinded	38	26	Type 2 diabetes	8-oxodG	Urine	HPLC-ECD	No difference in 8-oxodG between groups	[182]
1) Glutathione (1000 mg/d), 2) placebo	RCT	Double blinded	39	4	Healthy subjects	8-oxodG	Urine	ELISA	No difference in 8-oxodG between groups	[165]
1) Placebo, 2) lycopene (30 mg/d)	RCT	Double blinded	39	8	Healthy subjects with mildly elevated plasma cholesterols	8-oxodG	Urine	ELISA	Reduction in 8-oxodG within lycopene (30 mg/d) treated group. No information regarding differences between groups	[142]
1) Hesperidin (500 mg/d), 2) placebo	RCT	Double blinded	60	6	Type 2 diabetes	8-oxodG	Serum	ELISA	Hesperidin treatment decreased 8-oxodG compared to placebo treatment	[273]
1) Mind master (vitamin suppl.), 2) placebo	RCT	Double blinded	58	8	Healthy subjects	8-oxodG	Urine	ELISA	Vitamin suppl. significantly decreased 8-oxodG compared to placebo	[274]
1) Coenzyme Q10, 2) no treatment	CT with matched controls	Open label	48	208	Children with Down syndrome	8-oxodG + 8-oxoGuo	Urine	UPLC-MS/MS	Coenzyme Q10 treatment did not affect 8-oxodG or 8-oxoGuo compared to control	[45]
Folic acid (5 mg/d)	Uncontrolled before-after	NA	30	4	Type 2 diabetes	8-oxodG	Salivary	ELISA	Folic acid treatment decreased salivary 8-oxodG concentration	[116]
Hemodialysis 1) with α-tocopherol coated filters 2) without α-tocopherol coated filters	Uncontrolled before-after	NA	18	39	Chronic kidney disease (non-diabetes (n = 10) and diabetis (n = 8)	8-oxodG	Serum	ELISA	Reduction in 8-oxodG concentration when treated with α-tocopherol coated filters	[127]

Table 1 summarizes intervention studies investigating the effects of antioxidant therapy on 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and/or 8-oxo-7,8-dihydroguanosine (8-oxoGuo). If months were reported as study duration, then 1 months = 4 weeks, 3 months = 13 weeks. Abbreviations: d, day; ECD, electrochemical detection; ELISA, enzyme-linked immunosorbent assay; GC, gas chromatography; HPLC-MS/MS, high performance liquid chromatography tandem mass spectrometry; RCT, randomised controlled trial; Suppl., supplementation; UPLC, ultra-performance liquid chromatography.

[a] No correction for urinary flow.

[b] The authors state that they measure 8-oxoGuo, but the method describes that they measure 8-oxodG.

Table 2
Anti-hyperglycemic agents.

Intervention	Study design	Blinding	Total no. of subjects	Study duration (weeks)	Subject characteristics	Marker	Human body fluid	Analysis method	Results	Reference
1) Metformin (1500 mg/d), 2) dapagliflozin (5 mg/d) + metformin (750 mg/d)	RCT	Open label	74	16	Type 2 diabetes	8-oxodG	Urine	Not specified	Dapagliflozin treatment decreased 8-oxodG compared to metformin treatment	[225]
1) Metformin (obese = 2000 mg/d; non-obese = 1500 mg/d), 2) placebo	RCT	Double blinded	110	13	Polycystic ovarian syndrome	8-oxodG	Serum	ELISA	Metformin treatment decreased 8-oxodG compared to placebo, however only among obese participants	[97]
1) Pioglitazone (15–45 mg/d), 2) glimepirid (2–6 mg/d) or gliclazide (80–240 mg/d)	RCT	Open label	98	12	Type 2 diabetes	8-oxodG	Urine	Not specified	Pioglitazone treatment significantly decreased 8-oxodG compared to sulfonylurea group. However, reduction in 8-oxodG was observed within both groups	[227]
1) Glimepirid (1.5 mg/d), 2) glibenclamide (1.25 mg/d) (+nutritional guidance in both groups)	RCT	Open label	40	26	Type 2 diabetes	8-oxodG	Urine	ELISA	Significant difference in 8-oxodG between treatment groups. Significant increase in 8-oxodG within glibenclamide treated group	[138]
Insulin pump	Uncontrolled before-after	NA	80	2	Type 2 diabetes	8-oxodG	Serum	ELISA	Insulin pump treatment decreased 8-oxodG concentration	[122]
Canagliflozin (100 mg/d)	Uncontrolled before-after	NA	15	4 days	Type 2 diabetes	8-oxodG	Urine	Not specified	Canagliflozin treatment decreased 8-oxodG	[232]
Candesartan (12 mg/d) + pioglitazone (15 mg/d)	Uncontrolled before-after	NA	41	26	Type 2 diabetes + hypertension	8-oxodG	Urine	HPLC (detection method not specified)	No difference in 8-oxodG following treatment with candesartan and pioglitazone	[174]
Linagliptin (5 mg/d)	Uncontrolled before-after	NA	30	13	Type 2 diabetes	8-oxodG	Urine	Not specified	No difference in 8-oxodG following treatment with linagliptin	[228]

Table 2 summarizes intervention studies investigating the effects of anti-hyperglycemic agents on 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and/or 8-oxo-7,8-dihydroguanosine (8-oxoGuo). If months were reported as study duration, then 1 months = 4 weeks, 3 months = 13 weeks. Abbreviations: d, day; ELISA, enzyme-linked immunosorbent assay; HPLC, high performance liquid chromatography; RCT, randomised controlled trial.

Table 3
Lipid lowering therapy.

Intervention	Study design	Blinding	Total no. of subjects	Study duration (weeks)	Subject characteristics	Marker	Human body fluid	Analysis methods	Results	Reference
1) Atorvastatin (10 mg/d), 2) atorvastatin (40 mg/d)	RCT	Double blinded	123	52	Ischemic cardiomyopathy	8-oxodG	Serum	ELISA	Atorvastatin treatment (40 mg/d) decreased 8-oxodG compared to atorvastatin treatment at lower dosage (10 mg/d)	[111]
1) Rosuvastatin (2.5–10 mg/d), 2) standard care	RCT	Open label	104	26	Type 2 diabetes	8-oxodG	Urine	ELISA	Rosuvastatin treatment decreased 8-oxodG compared to standard care	[150]
1) Atorvastatin (10 mg/d), 2) simvastatin (40 mg/d)	RCT	Single blinded	30	12	Type 1 diabetes, type 2 diabetes, obesity, and/or hypertension	8-oxodG	Urine	LC-MS/MS	No difference in 8-oxodG between treatment group	[185]
1) Lovastatin (20 mg/d), 2) hypolipemic diet	RCT	Open label	58	26	Hemodialyzed patients	8-oxodG	Serum	ELISA	No difference in 8-oxodG between groups, but within lovastatin treated group 8-oxodG was decreased	[119]
1) Placebo, 2) ezetimibe (10 mg/d) + simvastatin (20 mg/d), 3) rosuvastatin (20 mg/d)	RCT	Double blinded	74	16	Type 2 diabetes	8-oxodG	Plasma	ELISA	No difference in 8-oxodG between treatment groups	[109]
1) Simvastatin (40 mg/d), 2) placebo	RCT	Double blinded	39	2	Healthy males	8-oxodG + 8-oxoGuo	Urine	UPLC-MS/MS	No difference between treatment groups in urinary excretion of 8-oxodG and 8-oxoGuo	[237]
1) Pitavastatin (2 mg/d), 2) pitavastatin (2 mg/d) + ezetimibe (10 mg/d)	RCT	Not specified	20	23	Chronic kidney disease and hypercholest-erolemia	8-oxodG	Urine	ELISA	No difference in 8-oxodG between groups. Reduction in 8-oxodG within both groups.	[161]
Rosuvastatin (2.5 mg/d)	Uncontrolled before-after	NA	34	12	Dyslipidemia ± type 2 diabetes	8-oxodG	Urine	ELISA	Rotavasatin treatment decreased 8-oxodG	[145]
Pitavastatin (2 mg/d)	Uncontrolled before-after	NA	45	52	Type 2 diabetes	8-oxodG	Urine	ELISA	Pitavastatin treatment decreased 8-oxodG	[146]
Pitavastatin (2 mg/d)	Uncontrolled before-after	NA	16	26	Coronary artery disease	8-oxodG	Urine	ELISA	Pitavastatin decreased postprandial 8-oxodG, but not pre-prandial 8-oxodG	[275]
Atorvastatin (10 mg/d)	Uncontrolled before-after	NA	19	22	Hypercholest-erolemia	8-oxodG	Urine	ELISA	No difference in 8-oxodG following atorvastatin treatment	[147]

Table 3 summarizes intervention studies investigating the effects of lipid lowering therapy on 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and/or 8-oxo-7,8-dihydroguanosine (8-oxoGuo). If months were reported as study duration, then 1 months = 4 weeks, 3 months = 13 weeks. Abbreviations: d, day; ELISA, enzyme-linked immunosorbent assay; LC-MS/MS, liquid chromatography tandem mass spectrometry; RCT, randomised controlled trial; UPLC, ultra-performance liquid chromatography.

measurement in serum samples, and so, the results should be interpreted carefully [107]. Selenium treatment has been investigated among patients with breast cancer and healthy BRCA carriers with a decent sample size demonstrated no effect of selenium treatment on 8-oxodG analyzed by GC-MS [220]. This is in contrast to other studies investigating selenium treatment, where one study showed a within group reduction in 8-oxodG, but did not report differences between groups [221] and another study demonstrated a between-group reduction in the urinary excretion of 8-oxodG, but did not correct the concentration for urinary flow [222]. Supplementation with other antioxidants such as α-lipoic acid, glutathione, and coenzyme Q10 has not shown any effect on 8-oxodG [45,165,182,217]. Details regarding study designs and results for the mentioned and other potential antioxidants are summarized in Table 1.

In summary, the traditionally antioxidant therapies do not seem to affect 8-oxodG excretion consistent with previous large RCTs that did not demonstrate any beneficial effects of antioxidant supplementation on cancer development [31,32,34].

9.2. Pharmaceutical drugs

Several pharmaceutical drugs have been proposed to affect oxidative stress. Given the multiple sources that could generate reactive species or antioxidants, it seems plausible that pharmaceutical drugs could affect some of these, thus, explaining the beneficial or potentially harmful effects of a given drug.

Patients with T2D seem vulnerable to oxidative nucleic acid modifications; thus, the next section will focus on the pharmaceutical drug groups used in this patient group and their potential effect on oxidatively generated modifications of nucleic acids.

9.2.1. Anti-hyperglycemic agents

Several anti-hyperglycemic agents have been proposed to affect oxidative stress and, thus, provide pleiotropic effects on the management of T2D [223]. However, in the case of effects on 8-oxodG, the evidence is sparse. Table 2 summarizes the studies investigating the effects of glycemic agents on 8-oxodG.

Metformin is the first-line drug for the management of hyperglycemia in patients with T2D [224]. The effect of metformin on 8-oxodG cannot be concluded from the conducted studies. One study found a decrease in 8-oxodG following metformin treatment compared to the placebo treatment in patients with polycystic ovarian syndrome, but only among obese patients [97]. The study analyzed serum samples using an ELISA method, due to which the result has limited value. In contrast to this finding, another study with no information regarding the analysis method used metformin as a control group and found that urinary excretion of 8-oxodG/creatinine changed from (mean ± SD) 4.8 ± 2.0 to 5.8 ± 2.3 ng/mg following 16 weeks of metformin treatment [225]. Sulfonylureas have been suggested to exert different effects on oxidative stress depending on the investigated drug, whereas gliclazide in contrast to glibenclamide and glimepiride, does not seem to stimulate ROS production [226]. In terms of the effect on 8-oxodG, one study found that glibenclamide increased the urinary excretion of 8-oxodG compared to glimepiride [138], whereas another study had a group receiving either glimepiride or gliclazide, that decreased 8-oxodG within the group, but not as much as the other group receiving pioglitazone [227]. The effects of different individual sulfonylureas on oxidatively generated modifications of nucleic acids should be further investigated using appropriate analysis techniques. A recent study examined the effect of three months treatment with the dipeptidyl peptidase-4 (DPP-4) inhibitor, linagliptin, in an uncontrolled before-after study in patients with T2D. The study did not demonstrate any significant change in the urinary excretion of 8-oxodG [228].

The newer classes of anti-diabetic drugs (i.e., sodium glucose co-transporter 2 inhibitor (SGLT2i) and glucagon like peptide 1 (GLP-1) analogues) that have revealed beneficial effects on cardiovascular outcome [229–231] should be investigated as their effects on oxidative stress might explain some of their cardioprotective effects. The effect of SGLT2i on 8-oxodG has been investigated in two studies, that unfortunately do not mention the analysis technique used. The first study found a decrease in the urinary excretion of 8-oxodG compared to metformin treatment [225], whereas the second was an uncontrolled before-after study reporting that canagliflozin decreased the urinary excretion of 8-oxodG after four days of treatment [232]. Given the association between 8-oxoGuo and disease progression among patients with T2D [7–9] it will be interesting to explore whether SGLT2i decreases 8-oxoGuo and this is currently being investigated [73]. Liraglutide has shown beneficial effects on lipid peroxidation in patients with T2D [233], thus, prompting investigation of its effect on oxidatively generated modifications of nucleic acids in patients with T2D.

In summary, conflicting results exist regarding the effect of metformin and sulfonylurea treatment on 8-oxodG. Additional investigations on the drugs as well as evaluation of the newer drug classes are to be investigated before any conclusions can be made of the effects of anti-hyperglycemic agents on oxidatively generated nucleic acid modifications.

9.2.2. Lipid lowering drugs

Statin treatments are known to reduce major coronary events (non-fatal myocardia infarcts or coronary heart disease-caused death), cases of coronary vascularization, and cases of stroke [234]. The effect is mainly mediated through reduction of plasma cholesterol levels, but additional beneficial effects on inflammation and oxidative stress may also contribute [235]. A recent cross-sectional study found that statin users had 4.3–6.0% lower urinary excretion of 8-oxodG compared to non-statin users, whereas 8-oxoGuo levels were similar among the groups. In particular, statin users ≥60 years, with hypertension, or declined kidney function showed lower urinary excretion of 8-oxodG compared to the non-users [236].

Several studies have investigated the effect of lipid lowering drugs on 8-oxodG (Table 3). Since the cross-sectional study suggested that statin treatment may only decrease 8-oxodG excretion by a few percentages [236], most studies would not be able to detect such a small effect given their sample sizes. One of the studies calculated a sample size of 20 in each group as sufficient to detect an effect size of 20% [237]. Two studies with a larger study population (i.e., n > 100) found that statin treatment decreased the 8-oxodG levels in both serum and urine compared to a low dose of the same statin or standard care, respectively, using ELISA for the analysis in both studies [111,150]. The studies that used LC-MS/MS for analysis did not find any effect on the urinary excretion of 8-oxodG, but both had relatively small sample sizes (i.e., n = 30 and n = 39) [185,237]. Uncontrolled before-after studies as well as additional RCTs showed within group reduction of 8-oxodG [119,145,146,161].

Despite, the low quality of the analysis method in most studies, the results indicate that statin treatment seems to have an effect albeit a minor one on 8-oxodG excretion.

9.2.3. Anti-hypertensive agents

Hypertension is a known risk factor for cardiovascular disease as wells as diabetic microvascular complications [238]. Thus, blood pressure control is a cornerstone in the management and control of T2D [239]. Oxidative stress has been suggested to contribute to the development of hypertension [240]. A study found differences in the urinary excretion of 8-oxodG when comparing individuals 1) without hypertension, 2) with newly untreated hypertension, and 3) with treatment-engaged hypertension (using an ELISA method for analysis). They found significantly elevated urinary excretion of 8-oxodG among both groups of patients with hypertension. Furthermore, the treatment-engaged patients presented lower urinary excretion of 8-oxodG compared to treatment-naïve subjects [241]. Despite this, a careful interpretation is necessary given the cross-sectional study design and analysis method.

Table 4
Anti-hypertensive agents.

Intervention	Study design	Blinding	Total no. of subjects	Study duration (weeks)	Subject characteristics	Marker	Human body fluid	Analysis method	Results	Reference
1) Carvedilol (12.5 or 25 mg/d), 2) hydrochlorothiazide (12.5 or 25 mg/d) (Dosage depended on blood pressure)	RCT	Double blinded	38	8	Mild-moderate hypertension	8-oxodG	Plasma	ELISA	Reduction of 8-oxodG within carvedilol treated group, but not hydrochlorothiazide treated group. No information regarding differences between groups	[113]
1) Placebo, 2) irbesartan (150 mg/d), 3) irbesartan (300 mg/d)	RCT	Double blinded	50	104	Type 2 diabetes	8-oxodG + 8-oxoGuo	Urine	UPLC-MS/MS	No difference in 8-oxodG between groups. Within placebo and irbesartan (300 mg/d) treated groups urinary excretion of 8-oxodG was decreased	[187]
1) Losartan (100 mg/d), 2) Amlodipine (10 mg/d)	RCT	Not specified	130	52	Type 2 diabetes	8-oxodG	Serum + urine	ELISA	Losartan treatment significantly decreased 8-oxodG concentrations in both serum and urine compared to amlodipine treatment	[102]
1) Losartan (100 mg/d), 2) losartan (50 mg/d) + imidapril (5 mg/d)	RCT	Not specified	32	48	Type 2 diabetes	8-oxodG	Urine	ELISA	Losartan + imidapril combination therapy decreased 8-oxodG more than losartan monotherapy. However, a reduction in 8-oxodG was observed within both treatment groups	[242]
1) Olmesartan (10 mg/d), 2) amlodipine (5 mg/d)	RCT	Open label	70	52	Type 2 diabetes + hypertension	8-oxodG	Urine	ELISA	Reduction in 8-oxodG within the olmesartan treated group, but not following amlodipine treatment. No information regarding differences between groups	[140]
1) Efonidine (40 mg/d), 2) amlodipine (5 mg/d)	RCT	Open label	40	52	Type 2 diabetes + hypertension	8-oxodG	Urine	ELISA	Reduction of 8-oxodG within efonidine treated group, but not following amlodipine treatment. No information regarding differences between groups	[143]
1) Azelnidipine (16 mg/d), 2) nifedipine (40 mg/d)	RCT	Not specified	38	16	Type 2 diabetes + hypertension	8-oxodG	Urine	ELISA	Azelnidipine treatment decreased 8-oxodG compared to nifedipine treatment	[137]
1) Azelnidipine (16 mg/d), 2) amlodipine (5 mg/d)	RCT	Not specified	30	26	Mild chronic kidney disease + hypertension	8-oxodG	Urine	ELISA	Reduction in 8-oxodG within the azeldinipine treated group, but not following amlodipine treatment. No information regarding differences between groups	[162]
1) Candesartan (8 mg/d), 2) other anti-hypertensive agents that do not block RAS	RCT	Open label	132	12	Essential hypertension	8-oxodG	Urine	ELISA	Reduction in 8-oxodG within candesartan treated group. No information regarding differences between groups	[136]
Candesartan (12 mg/d) + pioglitazone (15 mg/d)	Uncontrolled before-after	NA	41	26	Type 2 diabetes + hypertension	8-oxodG	Urine	HPLC (detection method not specified)	No difference in 8-oxodG after treatment with candesartan and pioglitazone	[174]
Candesartan (12 mg/d) (replacement of prescribed antihypertensive drug)	Uncontrolled before-after	NA	46	26	Type 2 diabetes + hypertension	8-oxodG	Urine	HPLC (detection method not specified)	No difference in 8-oxodG following treatment with candesartan	[173]
Olmesartan or valsartan (no information regarding dosage)	Uncontrolled before-after	NA	13	16	Type 2 diabetes + hypertension	8-oxodG	Urine	ELISA	Reduction in urinary excretion of 8-oxodG following olmesartan/valsartan treatment	[139]

(*continued on next page*)

Table 4 (*continued*)

Intervention	Study design	Blinding	Total no. of subjects	Study duration (weeks)	Subject characteristics	Marker	Human body fluid	Analysis method	Results	Reference
Valsartan (40–80 mg/d)	Uncontrolled before-after	NA	26	13	Hypertension	8-oxodG	Urine	ELISA	Reduction in urinary excretion of 8-oxodG following valsartan treatment	[148]

Table 4 summarizes intervention studies investigating the effects of anti-hypertensive agents on 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and/or 8-oxo-7,8-dihydroguanosine (8-oxoGuo). If months were reported as study duration, then 1 months = 4 weeks, 3 months = 13 weeks. Abbreviations: d, day; enzyme-linked immunosorbent assay; HPLC, high performance liquid chromatography; RCT, randomised controlled trial; Suppl., supplementation; UPLC-MS/MS, ultra-performance liquid chromatography tandem mass spectrometry.

The results suggest that reduction in blood pressure and/or anti-hypertensive agents may decrease the urinary excretion of 8-oxodG. Quite a few studies (Table 4) have investigated the effects of anti-hypertensive agents on 8-oxodG, but again, most studies used an ELISA method for the analysis.

The only study that used an LC-MS/MS analysis method found that patients with T2D treated with irbesartan (300 mg/d) decreased urinary excretion of 8-oxodG within the group, but not when compared to placebo treatment. The sample size was relatively small (n = 50, separated in three groups) [187]; thus, a large effect size of irbesartan would be required to demonstrate any between-group effect. Renin-angiotensin system inhibitors (RASi) seem to affect the amount of generated 8-oxodG. A study examining 130 patients with T2D demonstrated decreased urinary excretion of 8-oxodG following losartan treatment compared to amlodipine treatment [102]. Uncontrolled before-after studies and RCTs demonstrated within-group reduction of 8-oxodG following treatment with angiotensin II receptor antagonists (i.e., olmesartan, candesartan, and valsartan) [136,139,140,148], however two studies showed no effect of candesartan treatment [173,174]. One study demonstrated that a combination of losartan (50 mg/d) and imidapril (5 mg/d) (an angiotensin converting enzyme inhibitor (ACEi)) decreased 8-oxodG to a greater extent compared to single administration of losartan (100 mg/d) [242]. Furthermore, the calcium channel blocker, azelnidipine, has been shown to decrease 8-oxodG compared to nifedipine treatment [137]. In line with this, another study demonstrated a within-group reduction in 8-oxodG following azelnidipine treatment, but did not report any between-group statistics [162]. In contrast to the mentioned anti-hypertensive agents, the calcium channel blocker amlodipine, has shown no effect on the urinary excretion of 8-oxodG [102,140,143,162].

In conclusion, the studies suggest that RASi and potentially azelnidipine may decrease 8-oxodG independently of the anti-hypertensive effects. However, given the fact that the results are based on studies using ELISA analysis methods, verification using a method with high specificity is warranted.

9.3. Lifestyle

Lifestyle has a major impact on disease development and progression [243,244]. However, lifestyle interventions are difficult for the individual to initiate, and are even more difficult to maintain; and for researchers, these are difficult to investigate.

The impact of dietary intervention on oxidatively generated modifications of nucleic acids are difficult to investigate in an unconfounded setting. Changes in a single dietary component may very likely change the remaining dietary intake. Thus, full provision of food is preferable. Furthermore, blinding of lifestyle interventions constitutes a major challenge. The blinding procedure is often difficult to evaluate as a reader and would be strengthened greatly if an evaluation of adequate blinding were published along with the results (i.e., surveying which allocation participants and investigators expect has been allocated).

9.3.1. Diets and beverages

Adherence to a Mediterranean diet (rich in e.g., fruits, vegetables, olive oil, and nuts) has shown an inverse association with mortality [245] and the RCT, PREDIMED demonstrated a reduction in the incidence of major cardiovascular events following a Mediterranean diet supplemented with extra-virgin olive-oil or nuts compared to a reduced-fat diet in patients with a high risk of cardiovascular disease [246]. The beneficial effects of the Mediterranean diet have been suggested to be mediated at least to some extent by the antioxidative properties of the diet [247]. An inverse association with mortality has also been found in other epidemiological studies investigating diets rich in antioxidants [248,249].

Table 5 summarizes the interventional studies that have

Table 5
Diet and beverages.

Intervention	Study design	Blinding	Total no. of subjects	Study duration (weeks)	Subject characteristics	Marker	Human body fluid	Analysis methods	Results	Reference
1) Agraz (200 g/d), 2) placebo (no polyphenols)	RCT (cross-over)	Double blinded	40	4	Metabolic syndrome	8-oxodg	Urine	ELISA	Reduction in 8-oxodG following agraz treatment compared to placebo treatment	[132]
1) Blueberry juice (240 ml/d), 2) ascorbic acid (1 g/d)	RCT	Open label	12	2	Healthy subjects	8-oxodG	Urine	HPLC-ECD	No difference in 8-oxodG between groups. Significant reduction within blueberry treated group	[276]
1) Red yeast rice and olive fruit extract (monacolin K: 10.82 mg/d; hydroxytyrosol: 9.32 mg/d), 2) placebo	RCT	Double blinded	49	8	Metabolic syndrome	8-oxodG	Urine	ELISA	No difference in 8-oxodG between groups	[149]
1) Nine cooking classes with focus on cruciferous vegetables + administration of fresh cruciferous vegetables, 2) conventional diet	RCT	Open label	69	3	Postmenopausal women	8-oxodG	Urine	ELISA	No difference in 8-oxodG between groups	[135]
1) Freeze dried blueberry powder (22 g/d), 2) Placebo	RCT	Double blinded	40	8	Postmenopausal women with pre- or stage 1 hypertension	8-oxodG	Plasma[a]	ELISA	Compared to placebo treatment, blueberry powder treatment decreased 8-oxodG after 4 weeks supplementation, but not after 8 weeks	[277]
1) Esterified 9,11-conjugated linoleic acids (3 g/d), 2) placebo oil	RCT	Not specified	28	12	Children with bronchial asthma	8-oxodG	Urine	HPLC-ECD	No difference in 8-oxodG between groups. Significant increase within both groups	[278]
1) Probiotic soy milk (200 ml/d), 2) soy milk (200 ml/d)	RCT	Double blinded	40	8	Type 2 diabetes	8-oxodG	Plasma	ELISA	No difference in 8-oxodG between groups	[124]
1) Fish oil (1 g/d), 2) placebo	RCT	Double blinded	40	13	Healthy smoking subjects	8-oxodG	Serum	ELISA	Reduction in 8-oxodG within fish oil treated group. No information regarding between group differences.	[126]
1) Conventional diet, 2) Conventional diet + non-alcoholic beer (660 ml/d)	RCT[b]	Open label	60	4	Post-partum women	8-oxodG	Plasma + urine	ELISA	Reduction in plasma, but not urine concentrations of 8-oxodG following non-alcoholic beer supplement compared to control	[106]
1) Information regarding healthy diet, 2) Information + vegetables (300 g/d) + plant oil (25 ml/d)	RCT	Open label	97	8	Type 2 diabetes & healthy subjects	8-oxodG + 8-oxoGuo	Urine	UPLC-MS/MS	No difference in 8-oxodG and 8-oxoGuo between groups	[186]
1) Mediterranean diet + extra virgin olive oil, 2) Mediterranean diet + mixed nuts, 3) advice on low fat	RCT	Open label	110	52	Metabolic syndrome	8-oxodG	Urine	HPLC-ECD	Significant reduction in 8-oxodG following both Mediterranean treated groups compared to control group	[184]
1) Probiotic yoghurt (200 g/d), 2) conventional yoghurt (200 g/d)	RCT	Single blinded	70	9	Pregnant women	8-oxodG	Serum	ELISA	No difference in 8-oxodG between groups, but significant reduction within probiotic yoghurt supplemented group	[279]
Exercise bout after 1) conventional diet, 2) conventional diet + blueberry supplement (250 g/d)	RCT	Open label	20	6	Healthy subjects	8-oxodG	Urine	LC-MS	No difference in 8-oxodG between groups	[189]
1) Conventional diet, 2) conventional diet + salmon (300 g/week)	RCT[b]	Open label	108	~18	Pregnant women	8-oxodG	Urine	ELISA	No difference in 8-oxodG between or within groups	[163]
1) Mediterranean diet + coenzyme Q10 (200 mg/d), 2) Mediterranean diet + placebo, 3) Western diet (saturated fatty acid-rich). (Cholesterol level kept constant)	RCT (cross-over)	Not specified	20	4	Healthy elderly subjects	8-oxodG	Plasma	ELISA	Significant reduction in 8-oxodG following both Mediterranean treatment groups compared to western diet. Significant reduction in 8-oxodG following combined Mediterranean and coenzyme Q10 treatment compared to Mediterranean + placebo treatment	[103]

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Table 5 (*continued*)

Intervention	Study design	Blinding	Total no. of subjects	Study duration (weeks)	Subject characteristics	Marker	Human body fluid	Analysis methods	Results	Reference
150 g/d cooked potato: 1) white fleshed russets, 2) yellow potatoes, and 3) purple-flesh potatoes (high levels of phenolic acids, anthocyanins, and carotenoids)	RCT	Open label	36	6	Healthy subjects	8-oxodG	Plasma	ELISA	Significant reduction in 8-oxodG following both yellow and purple-flesh potatoes supplementation compared to white potatoes supplementation	[123]
1) Control (recommendation to the American Hearth Associations dietary guidelines 2) same dietary recommendation + mixed nuts (30 g/d)	RCT	Open label	50	12	Metabolic syndrome	8-oxodG	Urine	HPLC-ECD	Signification reduction in 8-oxodG following nut supplementation compared to control group. However, reduction in 8-oxodG within both groups	[179]
1) Red wine (118 ml/d), 2) white wine (118 ml/d), 3) control (alcohol abstinence)[c]	RCT	Open label	36	26	Type 2 diabetes + nephropathy	8-oxodG	Urine	ELISA	Significant reduction in 8-oxodG following red wine supplement compared to white wine supplement and control	[159]
1) Enriched high dose of n-3 LC-PUFA, 2) commercial dairy products	RCT (cross-over)	Double blinded	21	12	Rheumatic arthritis	8-oxodG	Urine	HPLC-ECD	No difference in 8-oxodG between groups	[176]
1) Calorie restriction (20% energy deficit), 2) exercise (energy deficit 20%)	RCT	Open label	29	52	Healthy subjects	8-oxodG + 8-oxoGuo	Urine	HPLC-MS/MS	No difference in 8-oxodG or 8-oxoGuo between or within groups	[188]
1) Hot water extraction process from dried bonito broth (125 ml/d), 2) placebo	RCT	Double blinded	29	2	Healthy subjects	8-oxodG	Urine	ELISA	Significant reduction in 8-oxodG following dried bonito extract treatment	[280]
1) Olive oil refined (25 ml/d), 2) olive oil medium polyphenol refined (25 ml/d), 3) olive oil high polyphenol refined (25 ml/d)	RCT (cross-over)	Double blinded	182	3	Healthy subjects	8-oxodG + 8-oxoGuo	Urine	HPLC-MS/MS	Reduction in 8-oxodG, but not 8-oxoGuo following olive oil treatment. No difference between treatment groups	[250]
Plain boiled rice with 1) Dark soy sauce (30 ml), 2) placebo (food colorant)	RCT (cross-over)	Single blinded	24	4 h	Healthy subjects	8-oxodG	Urine	GC-MS	No difference in 8-oxodG between groups. However, reduction in 8-oxodG within placebo treated group	[281]
1) Cranberry juice (750 ml/d), 2) placebo	RCT	Not specified	20	2	Healthy subjects	8-oxodG	Urine	ELISA	No difference in 8-oxodG between groups. Reduction in 8-oxodG within both groups	[154]
1) Vegetables (600 g/d), 2) vitamin supplement containing vitamins and minerals equal to 1), 3) placebo	RCT	Not specified	43	3.5	Healthy subjects	8-oxodG	Urine	HPLC-ECD	No difference in 8-oxodG between groups. However, reduction in 8-oxodG within Mediterranean diet + virgin olive oil supplemented group	[282]
1) Mediterranean diet + virgin olive oil, 2) Mediterranean diet + washed virgin olive oil, 3) control (habitual diet)	RCT	Open label	90	13	Healthy subjects	8-oxodG	Urine	HPLC-ECD	No difference in 8-oxodG between groups. Significant reduction within washed virgin oil treated group	[177]
Beverage 3 ml/kg + exercise bout 1) Black grape (81.2 g/l), raspberry (93.0 g/l), red currant (39.2 g/l) 2) placebo	RCT	Double blinded	30	2 days	Healthy athlete subjects	8-oxodG	Urine	HPLC-ECD	Significant difference in urinary excretion of 8-oxodG between groups	[283]
1) Cranberry leaf extract beverage, 2) low-calorie juice cocktail, 3) placebo (~450 ml)	RCT (cross-over)	Double blinded	12	1 day	Healthy subjects	8-oxodG	Plasma	ELISA	No difference in 8-oxodG between groups	[284]
1) Placebo, 2) juice (red grape: bilberries (80:20), 330 ml/d), 3) smoothie (red grape: bilberries (80:20), 330 ml/d)	RCT (cross-over)	Double blinded	30	2	Healthy subjects	8-oxodG	Urine	ELISA	No differences in 8-oxodG within groups. No information regarding differences between groups	[129]
1) Ganoderma lucidum (225 mg/d), 2) placebo	RCT (cross-over)	Double blinded	39	26	Mild liver dysfunction	8-oxodG	Plasma	ELISA	Reduction in 8-oxodG following ganoderma lucidum treatment compared to placebo	[94]
1) Brussel sprout (300 g/d), 2) control (diet free of cruciferous vegetables)	RCT	Open label	10	3	Healthy subjects	8-oxodG	Urine	HPLC-ECD	No difference in 8-oxodG between groups. However, a significant within-group reduction of 8-oxodG was observed within the group supplemented with Brussel sprouts	[285]

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Table 5 (*continued*)

Intervention	Study design	Blinding	Total no. of subjects	Study duration (weeks)	Subject characteristics	Marker	Human body fluid	Analysis methods	Results	Reference
Physical activity after 1) Tomato juice (150 ml/d), 2) No treatment, 3) tomato juice (150 ml/d)	CT (cross-over)	Open label	15	5	Healthy subjects	8-oxodG	Serum	ELISA	Significant decreased serum concentrations of 8-oxodG following exercise when tomato juice supplementation was compared with no supplementation	[99]
1) Purple sweet potato leaves (PSPL) (200 g/d) 2) control/low polyphenol diet	CT (cross-over)	Open label	15	2	Healthy athlete subjects	8-oxodG	Urine	ELISA	During the control period 8-oxodG was significantly higher than baseline, PSLP consumption, and washout period	[156]
P. japanicum extract (189 mg/d) + saw palmetto extract (960 mg/d) ("Saw Palmetto + Isosamidin")	Uncontrolled before-after	NA	20	4	Males with untreated lower urinary tract symptoms	8-oxodG	Urine	Not specified	No difference in 8-oxodG	[286]
Dried apple and mandarin juice (40 g/d)	Uncontrolled before-after	NA	41	4	Obese children	8-oxodG	Urine*	ELISA	Reduction in 8-oxodG following dried apple and mandarin juice supplementation, but no correction for urinary flow	[287]
Fresh frozen black raspberries (32 g/d female; 45 g/d male)	Uncontrolled before-after	NA	10	26	Barret's esophagus	8-oxodG	Urine	ELISA	No difference in 8-oxodG	[288]
Fresh strawberries (500 g/d)	Uncontrolled before-after	NA	23	4	Healthy subjects	8-oxodG	Urine	ELISA	Reduction in 8-oxodG following strawberry supplementation. Normalized two weeks after end intervention	[251]

Table 5 summarizes intervention studies investigating the effects of diet and beverages on 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and/or 8-oxo-7,8-dihydroguanosine (8-oxoGuo). If months were reported as study duration, then 1 months = 4 weeks, 3 months = 13 weeks. Abbreviations: d, day; ECD, electrochemical detection; ELISA, enzyme-linked immunosorbent assay; GC, gas chromatography; HPLC-MS/MS, high performance liquid chromatography tandem mass spectrometry; RCT, randomised controlled trial; Suppl., supplementation; UPLC, ultra-performance liquid chromatography.

*No correction for urinary flow.

[a] DNA from plasma samples were purified and digested before determination.

[b] Inadequate randomization.

[c] The control group was specially selected (not randomised) as participants who were alcohol abstinent.

Table 6
Tea and coffee consumption.

Intervention	Study design	Blinding	Total no. of subjects	Study duration (weeks)	Subject characteristics	Marker	Human fluid	Analysis methods	Results	Reference
1) Coffee (4 cups/d = 32 g coffee/d), 2) coffee abstinence	RCT (cross-over)	Open label	37	4	Hepatitis C virus chronic liver disease	8-oxodG /dG	Plasma	HPLC-ECD	Reduction in 8-oxodG following coffee consumption compared to coffee abstinence	[252]
1) Green tea polyphenols (GTP) (500 mg/d), 2) GTP (1000 mg/d), 3) placebo	RCT	Double blinded	124	13	Healthy subjects	8-oxodG	Urine	HPLC-ECD	Reduction in 8-oxodG following both groups of GTP compared to placebo	[166]
1) Green tea (polyphenols 1010 mg/d), 2) black tea (polyphenols 80 mg/d), 3) water	RCT	Open label	103	3–8	Prostate cancer	8-oxodG	Urine	HPLC-ECD	Reduction in 8-oxodG following green tea supplementation compared to water. No difference between black tea and water	[178]
1) Decaffeinated black tea (4 cups/d), 2) decaffeinated green tea (4 cups/d), 3) water (4 cups/d) (1 cup = 1 tea bag (1.9 g) in 8 ounces water for 3 min)	RCT	Open label	120	17	Healthy smoking subjects	8-oxodG	Urine	ELISA	No difference in 8-oxodG between groups (when in all study participants were investigated together). Reduction in 8-oxodG within green tea supplemented group	[141]
1) Green tea catechin (GTC) free group (0 mg/d), 2) GTC low (80 mg/d), 3) GTC high (580 mg/d)	RCT	Double blinded	30	2	Healthy smoking subjects	8-oxodG	Plasma	ELISA	Reduction in 8-oxodG following GTC high dose supplementation compared to GTC free/control group	[118]
Exercise + 1) Green tea catechins (780 mg/d), 2) placebo	CT (cross-over)[a]	Open label	16	2 hours	Healthy subjects	8-oxodG	Urine	ELISA	No difference in 8-oxodG between groups. Within both treatment groups urinary excretion of 8-oxodG increased following exercise	[155]
Green tea pills (2 g leaf powder/d, 200 mg total polyphenols)	Uncontrolled before-after	NA	30	8	Alzheimer's disease	8-oxodG	Plasma	ELISA	Reduction in 8-oxodG following treatment	[128]

Table 6 summarizes intervention studies investigating the effects of tea and coffee consumption on 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and/or 8-oxo-7,8-dihydroguanosine (8-oxoGuo). If months were reported as study duration, then 1 months = 4 weeks, 3 months = 13 weeks. Abbreviations: d, day; ELISA, enzyme-linked immunosorbent assay; HPLC-ECD, high performance liquid chromatography electrochemical detection; RCT, randomised controlled trial.

[a] Inadequate randomization.

Table 7
Exercise.

Intervention	Study design	Blinding	Total no. of subjects	Study duration (weeks)	Subject characteristics	Marker	Human body fluid	Analysis methods	Results	Reference
1) Resistance training (1 h supervised, 2 times weekly), 2) resistance training + nutritional supplement, 3) cognitive training (two times weekly)	RCT	Open label	80	26	Healthy elderly subjects	8-oxodG + 8-oxoGuo	Urine	LC-MS/MS	No difference in 8-oxodG or 8-oxoGuo between or within groups	[258]
Two times 1 h per week 1) High-intensity (6 submaximal (85%) repetitions per exercise), 2) moderate-intensity (15 submaximal (70%) rep. per exercise, 3) control (no exercise)[a]	RCT	Open label	93	16	Healthy untrained, elderly subjects	8-oxodG	Urine	HPLC-ECD	Significant increase in 8-oxodG within high intensity group, but reduction in 8-oxodG within moderate-intensity group. No information regarding between group differences	[172]
Swimming: 1) 6x50 m, 2) 1x2000 m	RCT (cross-over)	Open label	30	1 day	Healthy athlete subjects	8-oxodG	Plasma	ELISA	Significant increase in 8-oxodG immediate after in 1x2000 m group compared to baseline and 6x50 m. Following 6x50 m no immediate increase in 8-oxodG was observed, however, 1 h after, 8-oxodG was increased compared to baseline and 1x2000 m. Twenty-four hour following the exercise bout, 8-oxodG concentrations was similar to baseline.	[112]
1) Continuous cycling (70% of VO2max), 2) intermittent dumbbell squatting (70% of 1 repetition max)	RCT (cross-over)	Open label	10	30 min	Healthy athlete subjects	8-oxodG	Serum	ELISA	No difference in 8-oxodG between groups	[110]
1) Standard care + exercise (individually based on disease, exercise specialist supervision), 2) standard care	CT	Open label	15	10	Cancer (heterogenic group)	8-oxodG	Plasma	ELISA	No difference in 8-oxodG between groups	[289]
Swimming (maximal intensity, freestyle 6x50 m)	Uncontrolled before-after	NA	14	2 days	Healthy athlete subjects	8-oxodG	Plasma + urine	ELISA	One hour after exercise bout plasma concentration of 8-oxodG was increased, but urinary excretion of 8-oxodG was similar as baseline	[114]
Military program (8–11 h vigorous exercise/day, 6 times weekly)	Observational	NA	23	4	Healthy athlete subjects	8-oxodG	Urine	HPLC-ECD	Significant increase in 8-oxodG among non-smokers, but not smokers	[167]
Ultra-marathon (330 km, altitude difference 24,000 m)	Observational	NA	25	Approxi-mately 111 hours	Healthy athlete subjects	8-oxodG	Urine[b]	ELISA	Significant increase in urinary excretion of 8-oxodG following the ultra-marathon	[133]
Regular resistance training (twelve exercises (i.e. to train all major muscle groups), three times weekly)	Uncontrolled before-after	NA	28	14	Healthy subjects	8-oxodG	Urine	ELISA	Reduction in urinary excretion of 8-oxodG	[144]
Progressive resistance strength training, twice weekly (80% of 1 repetition maximum, 8 repetitions, three times)	Uncontrolled before-after	NA	16	12	Rheumatic arthritis & healthy elderly subjects	8-oxodG	Urine	ELISA	Reduction in 8-oxodG among patients with rheumatic arthritis, no effect in healthy subjects	[257]
Two sets of 4x50 freestyle swimming (maximum intensity) separated by 10 min	Uncontrolled before-after	NA	32	1 day	Healthy athlete subjects	8-oxodG	Plasma	ELISA	Significant increase in 8-oxodG immediate after the second session, but not after the first session	[120]
Runners: 70 min/15 km running (usual exercise), Swimmers: 1500 m, interval/90 min (usual exercise)	Uncontrolled before-after (two cohorts)	NA	18	1 day	Healthy athlete subjects	8-oxodG	Urine	HPLC-ECD	No difference in 8-oxodG	[169]
Two sessions: 5 h cycling followed by 15 h rest and subsequent time trial (40 km)	Uncontrolled before-after	NA	7	1	Healthy athlete subjects	8-oxodG	Urine	HPLC-ECD	No difference in 8-oxodG	[181]
One-hour cycling (at 70% of VO2 max)	Uncontrolled before-after	NA	10	4 days	Healthy subjects	8-oxodG	Urine	ELISA	Significant increase in daytime (12 h) urinary excretion of 8-oxodG 24 h after exercise bout, but not nighttime (12 h) urinary excretion of 8-oxodG	[255]

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Table 7 (*continued*)

Intervention	Study design	Blinding	Total no. of subjects	Study duration (weeks)	Subject characteristics	Marker	Human body fluid	Analysis methods	Results	Reference
A graded exercise test (Bruce treadmill protocol)	Uncontrolled before-after	NA	29	1 day	Healthy subjects	8-oxodG	Plasma	ELISA	No difference in 8-oxodG	[256]

Table 7 summarizes intervention studies investigating the effects of exercise on 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and/or 8-oxo-7,8-dihydroguanosine (8-oxoGuo). If months were reported as study duration, then 1 months = 4 weeks, 3 months = 13 weeks. Abbreviations: d, day; ELISA, enzyme-linked immunosorbent assay; HPLC- ECD MS/MS, high performance liquid chromatography electrochemical detection; LC-MS/MS, liquid chromatography tandem mass spectrometry; RCT, randomised controlled trial.

[a] No measurement at the end of intervention in control group.

[b] creatinine adjusted urinary excretion of 8-oxodG immediate after exercise bout.

investigated the effects of various diets on 8-oxodG and 8-oxoGuo excretion rates. The effect of the Mediterranean diet on 8-oxodG excretion has been investigated in two studies. One study demonstrated a reduction in the urinary excretion of 8-oxodG (analyzed by HPLC-ECD) in patients with metabolic syndrome following a Mediterranean diet compared to the control group receiving advice on a low fat diet [184]. A second study used an ELISA method to analyze plasma samples. In agreement, the study found decreased concentrations of 8-oxodG following a Mediterranean diet compared to a western diet (with constant plasma cholesterol concentrations) [103]. In contrast to these finding, one study revealed no difference in the urinary excretion of 8-oxodG between Mediterranean diet and habitual diet in healthy subjects [177]. Many studies have examined the effect of single components from the Mediterranean diet on 8-oxodG. The effect of olive oils on 8-oxodG has been investigated in two studies. One study examined three olive oils (i.e., refined, medium polyphenol content, and high polyphenol content) and found that the olive oils decreased the urinary excretion of 8-oxodG with no difference between groups (analyzed by LC-MS/MS) [250]. Another study demonstrated no difference between olive oil treatment combined with Mediterranean diet and the controls in 90 healthy subjects; however, a reduction was observed within the group supplemented with virgin olive oil [177]. Supplementation with 30 g/d of mixed nuts together with dietary recommendation from the American Heart Association decreased the urinary excretion of 8-oxodG to a greater extent compared to the recommendations alone in patients with metabolic syndrome [179]. Red wine supplementation has been shown to decrease the plasma concentration of 8-oxodG, as measured by ELISA, compared to white wine and no supplementation [159]. Several fruits, vegetables, and berries have been investigated, wherein most studies demonstrated no effect on 8-oxodG excretion between groups. However, some berries have been shown to decrease 8-oxodG [132,251]. Thus, seasonal variation in 8-oxodG would be interesting to investigate and would also need to be considered in future studies as a possible confounder.

The findings of dietary interventions suggest an effect of the Mediterranean diet and to some extent, single components from the diet on 8-oxodG levels.

The antioxidant properties of tea and coffee consumption have also attracted focus. Table 6 summarizes the studies evaluating the effect of tea and coffee consumption on 8-oxodG. Two studies with decent study sample sizes (i.e., n = 124 and n = 103) both measured the urinary excretion of 8-oxodG by HPLC-ECD, and both found a decrease in the urinary excretion of 8-oxodG following green tea consumption compared to the placebo/control [166,178]. The same results were found in remaining studies evaluating green tea consumption; however, the evidence of these studies was not as strong, because the studies were designed as uncontrolled before-after or reported only within-group effects [128,141] and/or using plasma samples analyzed by an ELISA method [118,128]. A single study evaluated the short term effects of green tea catechins (i.e., 2 h) combined with exercise, and found no difference in 8-oxodG [155]. None of the studies found any effect of black tea on 8-oxodG [141,178]. To the best of our knowledge, only a single study evaluated the effects of coffee consumption on 8-oxodG. The study compared the plasma concentration of 8-oxodG/dG (analyzed by HPLC-ECD) following 4 months of 1) 4 cups of coffee or 2) abstinence in a cross-over setting, and found a reduction in 8-oxodG following coffee consumption compared to abstinence [252]. Interpretations should be made with cautions, since it is likely that the abstinence group might have a different pattern regarding diet, beverages, and other stimulants.

From these studies it seems like green tea, but not black tea consumption influences 8-oxodG. The effects of coffee consumption are an interesting topic for future research.

9.3.2. Exercise

The relationship between exercise and oxidative stress has been

examined extensively. Thus, this section is only a brief introduction to the relationship between exercise and oxidatively generated nucleic acid modifications.

In general, the effect of exercise could be split into acute and chronic effects. A single bout of physical activity is thought to generate reactive species and, thus, oxidative stress, whereas regular physical activity is thought to adapt the organism and decrease oxidative stress [253]. Various mechanisms responsible for the production of reactive species as well as adaption of the organism are proposed [254]. Thus, the redox response may differ depending on the investigated cellular compartment and it is presumable that the response regarding oxidized DNA and RNA differs. Table 7 summarizes the findings of exercise interventions on 8-oxodG and 8-oxoGuo levels. Most studies have investigated the effect of a single exercise bout and show conflicting results; however, the investigated exercise form and duration differ greatly. Some studies have found an increase in 8-oxodG measured in urine [133,255] and plasma [112,114,120], whereas others found no acute effects [110,169,181,256]. With respect to the chronic effect of exercise, again conflicting results are observed. One study demonstrate that low intensity exercise decreases 8-oxodG, whereas high intensity exercise increases 8-oxodG [172]. This is in agreement with the finding of an observational study showing that an intense military program increased the urinary excretion of 8-oxodG [167]. Two uncontrolled before-after studies found a reduction in the urinary excretion of 8-oxodG using ELISA [144,257] whereas a study with low intensity and duration found no effect on the urinary excretion of 8-oxodG (and 8-oxoGuo) measured by LC-MS/MS [258].

It is not easy to draw a clear picture describing the association between exercise and oxidatively generated modifications of nucleic acids, even though exercise seems to affect the generation. Exercise duration and intensity as well as the timing of the samples seems to be crucial. Furthermore, differences in study populations seem to provide different results [257].

9.3.3. Smoking

Cigarette tar contains high concentrations of reactive species [259] and a recent meta-analysis confirmed that smokers had a higher urinary excretion of 8-oxodG compared to non-smokers [91]. However, a recent observational study did not find any difference in the urinary excretion of 8-oxodG or 8-oxoGuo (measured by LC-MS/MS) in patients with T2D who smoked compared to patients with T2D who did not smoke [260]. This may suggest different susceptibility depending on metabolic states, whereas patients with T2D present high urinary excretion of both 8-oxodG and 8-oxoGuo compared to healthy subjects [261]. In healthy subjects, it is further demonstrated that smoking cessation causes reduction in the urinary excretion of 8-oxodG [262].

Smoking should, in general, be considered to cause oxidative DNA modifications; however, in subjects with a high background of DNA oxidation, this effect may be diminished or hidden.

9.4. Environmental factors

Exposure to air pollution, heavy metals, and pesticides promotes the generation of reactive species causing a redox imbalance [263–265]. Several studies have investigated the impact of environmental factors on 8-oxodG. Given the nature of the exposure, it is difficult to conduct RCT. Thus, the evidence is mainly based on observational studies with the limitations of such study designs.

Air pollution has been investigated in a controlled setting, where exposure to coarse and ultrafine, but not fine particles increased the urinary excretion of 8-oxodG at 1 h after exposure, but no difference was observed at 21 h after exposure [266]. In agreement, a cross-over RCT demonstrated lower plasma concentrations of 8-oxodG following a period with air filtration compared to open windows in homemakers living in a metropolitan area [267]. Furthermore, workers exposed to three days of diesel exhaust showed increased urinary excretion of 8-oxodG compared to non-exposed workers [134], and comparison of urinary excretion of 8-oxodG among petrol fillers and cashiers revealed higher urinary excretion of 8-oxodG among petrol fillers [131]. All studies used ELISA for analysis or did not mention the analysis method, which should be considered a clear limitation. Thus, interpretations should be made carefully.

Cross-sectional studies have investigated the urinary excretion of 8-oxodG among Chinese kitchen workers compared to workers with limited time in the kitchen. The studies found increased urinary excretion of 8-oxodG among the kitchen workers compared to the non-kitchen workers [170,175]. Statistical analysis further showed that 'working years' in the kitchen was associated with urinary excretion of 8-oxodG [175]. This suggest that exposure to deep-frying induces redox imbalance.

The relationship between exposure to heavy metals and DNA oxidation is sparsely investigated. However, a cross-sectional study showed similar serum concentrations of 8-oxodG among smelters and controls (i.e., non-smelters) [105]. Similarly, the association between pesticide exposure and DNA oxidation is not well explored. One cross-sectional study found elevated concentrations of 8-oxodG in genomic DNA of whole blood among pesticide sprayers compared to those in the controls. However, the exposed group predominantly included males, which may very well confound the results. Furthermore, the study found no association between pesticide metabolites concentrations and 8-oxodG, and 8-oxodG was measured using an ELISA method [268].

Thus, environmental factors seem to affect 8-oxodG, but much more work in this area is necessary to understand their relationship.

9.5. Surgery

The physiological stresses during and after surgery are, similar to acute exercise, thought to increase oxidative stress. Increased oxidative stress is hypothesized to worsen the prognosis following surgery [269]. A study in children compared the urinary excretion of 8-oxodG following cardiac catherization for diagnostic purposes and sedated echocardiography and found increased urinary excretion of 8-oxodG following cardiac catherization [152]. Two months after radical proctectomy, there was no change in the urinary excretion of 8-oxodG compared to that before surgery [157] and 6 months after laparoscopic gastric banding, a reduction in the urinary excretion of 8-oxodG was observed [104]. Comparison between surgical procedures (i.e., mini laparotomy *vs.* laparoscopic cholecystectomy) revealed no difference in the plasma concentrations of 8-oxodG between the procedures [96]. Rectus sheath block following midline laparotomy did not affect the plasma concentrations of 8-oxodG [95]. Interestingly, a study showed that patients with atrial fibrillation presented higher urinary excretion of 8-oxodG compared to subjects with sinus rhythm and that sinus rhythm restoration by both pharmaceutical and electrical intervention decreased the urinary excretion of 8-oxodG at ≥ 3 months after the procedure [158].

In summary, surgical procedures likely affect 8-oxodG differently, depending on the procedure. It is anticipated that the effect of surgical interventions diminishes with time post-surgery. Studies with repeated measurements following surgery would be of great interest in measuring oxidatively generated nucleic acid modifications.

9.6. Changes in iron metabolism

Divalent copper and iron enable production of ROS through the Fenton reaction. Since iron storage exceeds copper storage in humans, the relationship between iron metabolism and oxidative stress has attracted predominant focus [270]. Hereditary hemochromatosis is an autosomal recessive disease whereas regulation of iron uptake in the intestine is affected and iron storage within cells is increased. Patients with hereditary hemochromatosis present higher urinary excretion of 8-oxoGuo, but not 8-oxodG compared to healthy controls. Following

phlebotomy treatment urinary excretion of 8-oxoGuo is decreased whereas 8-oxodG is unaffected [11]. In agreement, another study found no effect following mineral supplementation with iron (27 mg/d) during pregnancy on the urinary excretion of 8-oxodG [164], but a study in patients on hemodialysis showed that intravenous iron infusion increased the serum concentration of 8-oxodG as measured by ELISA [98]. One might speculate, whether this results from an increase in 8-oxoGuo, as the majority of ELISA kits cannot discriminate between the 8-oxo species [211,212].

The findings suggest that increased iron concentrations affect RNA oxidation more than DNA oxidation. This is an example of the differences existing between RNA and DNA oxidation, emphasizing the importance of measuring both processes in clinically relevant settings.

10. Summary and future directions

Oxidatively generated modifications of nucleic acids are associated with different diseases. In particular, DNA oxidation is predominantly associated with cancer development and RNA oxidation with disease progression in patients with T2D. Most studies have focused on oxidatively generated modifications of nucleic acids by investigating DNA oxidation and not RNA oxidation. RNA has emerged in its conceptual role from a 'silent messenger' to an 'active component,' and we are convinced that future studies will focus on both DNA oxidation and RNA oxidation. The intracellular location of RNA leads us to hypothesize that reactive species produced by mitochondria contribute more to oxidatively generated modifications of RNA than of DNA. Thus, we consider that the right strategy to investigate interventions that modify RNA oxidation would be through investigating interventions that may modify mitochondrial activity (e.g., a shift in dietary composition, basic metabolic rate, and physical activity). However, given the current evidence of studies trying to modify DNA oxidation, some obvious studies would be to investigate the effect of lipid lowering therapy, RASi, Mediterranean diet, environmental factors, and smoking cessation on RNA oxidation. To further understand the mechanism that causes DNA and RNA oxidation, it is important to conduct mechanistic studies evaluating the effect of NADPH oxidase inhibitors, xanthine oxidase inhibitors, and mitochondrial complex modulators. Furthermore, the contribution from the nucleotide pool to the excretion of 8-oxodG and 8-oxoGuo needs to be clarified along with the mechanism of how the cell excretes oxidized nucleosides.

RNA oxidation measured by urinary excretion of 8-oxoGuo possesses great potential for clinical usage. Urinary excretion of 8-oxoGuo has been demonstrated as an independent, prognostic marker of all-cause mortality [7–9] and cardiovascular mortality [9,66] in patients with T2D. The next major target is to identify how to decrease the urinary excretion of 8-oxoGuo, and if so, what are the long-term effects of reducing the urinary excretion of 8-oxoGuo in patients with T2D on hard endpoints i.e., mortality and cardiovascular events.

Finally, we provide the following simple advice to those who plan to conduct clinicals studies measuring oxidatively generated modifications of nucleic acids:

1. *Consider your analysis method and ensure the appropriate laboratory procedures*
   The majority of ELISA kits cannot discriminate between 8-oxodG, 8-oxoGuo, and 8-oxo-7,8-dihydroguanine (8-oxoGua) [211,212] and may cross-react with urea [211]. Compared to LC-MS/MS, ELISA provides twice as high concentrations in urine and up to 10,000-fold higher concentrations in plasma and is unable to identify clinical relevant differences in 8-oxodG excretion that are detectable with LC-MS/MS metodology [91]. Presently, the specificity of the ELISA method is so low that it cannot be recommended.
2. *Consider the body fluid used and its interpretation*
   Plasma concentrations of 8-oxo-nucleosides are influenced by kidney function, similar to creatinine and may reflect kidney function more than the level of oxidatively generated modifications in nucleosides. When measuring oxidized nucleosides in the urine, it is necessary to correct for urinary flow, e.g., urine volume (24-h), -creatinine, or -density considering the strengths and limitations of each correction method.
3. *Consider the study population and study size*
   Oxidative stress differs between study populations and the response to an intervention on oxidatively generated modifications of nucleic acids may very well differ between the investigated study populations [167,187]. Ensure that the investigated study population enables extrapolation of study results to the relevant populations and be aware of potential factors that may confound the result (e.g., age, sex, medication, lifestyle habits, and environmental factor). Furthermore, many interventions may only modify oxidatively generated nucleic acid modifications by few percentages but may still be clinically relevant [236]. If possible, provide a sample size that is large enough to detect effect sizes of 5–10% or at least use analysis and study design methods that enables the results to be included in a meta-analysis.
4. *Report your study design and results so that others can reproduce your findings*
   Reporting the study design and results in accordance with the CONSORT guidelines is now becoming a standard practice [271]. However, there are still many studies with insufficient information on study design, due to which results cannot be reproduced. Defining your endpoints as primary, secondary, and post-hoc is also important.
5. *Define a statistical plan and ensure appropriate statistical analysis*
   The final, but essential point is to consider the importance of statistical analysis as well as to define a statistical plan before conducting the study. Several of the investigated studies in this review have not reported between-group statistics. An appropriate statistical analysis is just as important as the study design and laboratory analysis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.freeradbiomed.2019.09.030.

Declaration of interest

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