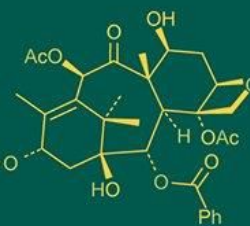


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Oxidative stress and redox biomarkers in clinical practice: Implications for cardiometabolic and inflammatory diseases: A review study

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Abstract

The pathogenesis of cardiometabolic and inflammatory diseases, including type 2 diabetes mellitus, cardiovascular disease, metabolic syndrome, and hypertension, is centrally related to oxidative stress and the redox imbalance. Data regarding 30 peer-reviewed articles published in 2014-2025 was synthesized in the current systematic review to assess the clinical use of redox biomarkers in risk stratification, disease monitoring, and therapeutic decision-making. The data found that protein-adjusted free thiols, homocysteine, lipid peroxidation products, and antioxidant enzyme activity were powerful prognostic factors of cardiovascular and all-cause mortality, and that there were distinct sex differences in the biomarker efficacy. According to the recent results, the joint analysis of the redox indices and inflammatory mediators, as well as genetic polymorphisms, is also useful to optimize risk stratification models. Despite these positive trends, challenges in standardization of analytical procedures, development of strong reference ranges and clinical translation of biomarker discoveries are still present. Based on this, the present review is a critical evaluation of existing evidence and outline of future studies in the area of redox biomarkers of cardiometabolic medicine.

Keywords: Redox biomarkers, oxidative stress, cardiometabolic diseases, inflammation

1. Introduction

The most frequent causes of morbidity and mortality in the world are cardiometabolic diseases, such as type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), metabolic syndrome, and hypertension. The pathophysiology is complex, and it involves a complex interaction between metabolic dysregulation, chronic inflammation, endothelial dysfunction, and oxidative stress [1]. As a pathological process, oxidative stress has been described as the imbalance in production of reactive oxygen species (ROS) and the ability to counteract the products of the activity through antioxidant defenses [2, 3]. The clinical assessment of oxidative stress using redox biomarkers has the potential to advance the risk stratification, early diagnosis, longitudinal assessment of treatment response, and identify new potential therapeutic targets [4, 5]. However, the development of redox biomarkers into clinical practice continues to face significant barriers in form of analytical variability, insufficient standardization and the lack of validation in nonhomogeneous populations [1]. Recent advances in the discovery of biomarkers, along with the advanced high-throughput analysis platforms and large-scale prospective cohort studies, have produced new information on the clinical relevance of redox biomarkers in cardiometabolic medicine [2, 6]. The current review brings together current evidence that has been identified relating to oxidative stress and redox biomarkers in clinical cases, especially in terms of their implications on cardiometabolic and inflammatory disorders. It questions the biological basis of redox dysregulation, evaluates diagnostic and prognostic capabilities of the well-known and emerging biomarkers, reflects on their clinical uses in a continuum of different pathologies, and identifies gaps of knowledge that should be addressed in future studies.

2. Background and Theoretical Foundations

2.1 Oxidative Stress in Cardiometabolic Pathophysiology

Excessive levels of reactive oxygen and nitrogen species (ROS and RNS, respectively) that overcome the endogenous antioxidant protective mechanisms provoke oxidative stress.

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Various cellular sources generate ROS; they encompass mitochondrial electron transport chains, NADPH oxidases, xanthine oxidase as well as uncoupled nitric oxide synthase [7, 8]. Finally, in cardiometabolic diseases, constant hyperglycemia, dyslipidemia, insulin resistance and inflammatory activation promote a pro-oxidant environment that contributes to the continuation of cell damage [9, 10]. The effects of oxidative stress are many and they affect the integrity of the DNA, the functioning of the proteins and stability of the lipid membrane. Oxidative alteration of low-density lipoprotein (LDL) aids in the formation of foam cell and atherosclerotic plaque [11]. Endothelial dysfunction occurs through the action of ROS which reduces the bioavailability of nitric oxide leading to vasoconstriction, platelet activation, and thrombosis [12]. In addition, oxidative stress activates pro-inflammatory pathways, including nuclear factor-kappa B (NF- κ B) and mitogen-activated protein kinases (MAPKs), thus creating a vicious circle of inflammation and oxidative injury [13, 14].

2.2 Redox Signaling and Disease Mechanisms

Along with its detrimental functions, ROS play a central role as signaling molecules in physiological functions, such as the proliferation, differentiation, and immune reactions of cells [15]. The idea of "redox signaling" takes into consideration that controlled production of ROS at physiological levels regulates gene expression, enzyme activity and cellular metabolism [16]. The alteration of the redox balance in cardiometabolic diseases provokes a shift in the physiological signaling to the pathological oxidative injury [17]. The expression of antioxidant response elements and cytoprotective genes are coordinated by key redox-sensitive transcription factors, such as nuclear factor erythroid 2-related factor 2 (Nrf2) [18]. Polymorphisms in Nrf2 and associated redox-regulatory genes predispose individuals to oxidative stress and the presence of cardiometabolic disease [18]. These molecular mechanisms are elucidated and constitute the conceptual framework of creating specific therapeutic interventions and interpreting the biomarker data in clinical practice [19, 20].

3. Redox Biomarkers in Clinical Practice

3.1 Free Thiols and Sulfhydryl Groups

One of the most functionally important redox buffers that is found in high concentrations in human plasma is free thiols (sulfhydryl groups, R-SH). Protein-adjusted free thiol levels reflect the total body redox environment and have been linked in large prospective studies to cardiovascular reactions [2]. In the cohort of the PREVEND, 5,955 individuals, protein-adjusted R-SH levels were significantly associated with a lower probability of cardiovascular events in men (HR 0.63, 95% CI 0.40-0.99, $p = 0.045$) and with a lower probability of all-cause mortality (HR 0.52, 95% CI 0.32-0.85, $p = 0.009$) [2]. Free thiol prognostic value is applicable in a variety of cardiometabolic disorders. Lower levels of thiols (in individuals with type 2 diabetes, metabolic syndrome and known cardiovascular diseases) have been reported and the changes are related to the severity and complications of the disease [6, 9]. The practical benefits of measurement of free thiols are relative stability of the measurement in archived samples, and the possibility of integration with high-throughput measurement platforms [2]. Nevertheless, standardization of assay procedures and definition of population-specific reference standards are still

urgent to apply in a routine clinical practice [1].

3.2 Homocysteine

Homocysteine, a sulfur-based amino acid product of the methionine metabolism, acts as a biomarker and a catalyst of the oxidative stress and dysfunction of the vessels. High homocysteine levels promote production of ROS, cause endothelial damage, and thrombotic events in several mechanistic pathways [2, 21]. The potential cohort studies have created close correlations between the levels of homocysteine and cardiovascular risk with sex-dependent differences in predictive value [2]. In PREVEND study, an increase in homocysteine levels was an indicator of cardiovascular events among men (HR 1.58, 95% CI 1.20-2.08, $p = 0.001$) and higher mortality rate of all causes among men and women (HR 2.30, 95% CI 1.14-3.76, $p < 0.001$ in women) [2]. In patients with type 2 diabetes, both microvascular and macrovascular complications, such as nephropathy, retinopathy and coronary artery disease, are related to homocysteine levels [4, 10]. Nevertheless, contradictory cardiovascular results have been found with randomized trials of homocysteine-reduction interventions using B vitamins, indicating that homocysteine level may be more a risk indicator than a causal agent [21].

3.3 Lipid Peroxidation Products

Lipid peroxidation, which refers to the oxidative breakdown of polyunsaturated fatty acids in the cell membranes, produces a broad range of bioactive aldehydes and other like compounds which act as sensitive effects of oxidative damage [11]. The malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and the F2-isoprostanes are the most widely studied of such biomarkers in cardiometabolic studies [11]. Ito *et al.*, have performed an extensive analysis of measurement approaches in lipid peroxidation and the relevance of the methods in clinical settings of diabetes, atherosclerosis, and chronic inflammation [11]. High levels of lipid peroxidation products relate to an increase of inadequate glycemic control, insulin resistance, and diabetic complications occurring in individuals with T2DM [4, 11]. Other lipid peroxidation products such as oxidized LDL particles play a direct role in the development and instability of atherosclerotic plaques in cardiovascular disease [11, 12]. High-resolution analysis methods, especially methods involving mass spectrometry, have improved the specificity and sensitivity of such measurements; however, there are still issues with the handling of the sample and standardisation of methodological issues [11].

3.4 Antioxidant Enzymes and Defense Systems

The main cellular defence system to oxidative stress is made up of endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), and glutathione reductase. The analysis of enzyme activities and concentrations complements the data on the direct indicators of oxidative damage [3, 5]. Extracellular superoxide dismutase (ecSOD) plasma level and SOD3 gene polymorphisms as predictors of cardiovascular events in diabetes have been examined. Mohammadi *et al.*, established that SOD3 allelic variants mediate the risk of myocardial infarction and general mortality in patients with type 1 and type 2 diabetes [3]. Their results emphasize the fact that genetic polymorphisms, enzymatic activity and clinical outcomes interact in complex ways and thus the

need to use both genetic and biochemical determinants in the assessment of antioxidant capacity [3]. The main intracellular thiol antioxidant is glutathione which is in reduced (GSH) and oxidised (GSSG) form; GSH/GSSG ratio is a sensitive indicator of cellular redox state [5, 14]. The changes in the metabolism of glutathione have been reported throughout the range of cardiometabolic ailments, with lessening of GSH levels and GSH/GSSG ratios being linked with severity of the illness and development of complications [14, 16].

3.5 Emerging and Novel Biomarkers

Along with the classic indicators of oxidative stress, there are a number of novel biomarkers that have potential in the clinical environment. Gamma-glutamyltransferase (γ -GT) is a hepatic enzyme that is also a predictor of cardiovascular events in metabolically predisposed people in addition to being a marker of oxidative stress [2, 17]. Bilirubin is an endogenous antioxidant that has an inverse relationship with cardiovascular risk as well as sex-specific effects observed in population analysis [2, 17]. Bilirubin and γ -GT in combination have been considered as a combination of biomarkers predictive of cardiovascular complications in type 2 diabetes. Al-Suhaimi *et al.*, analyzed this combination of biomarkers and found out complicated interactions that could help in increasing the risk stratification in comparison with what each of those markers alone could do [17]. MicroRNAs, especially miR-21 and miR-126, have become new circulating biomarkers which have been associated with redox, inflammation, and vascular injury in diabetics [6]. These non-coding RNAs also regulate oxidative stress outcomes and endothelial activity with potential diagnostic use as well as therapeutic options [6].

4. Clinical Applications in Cardiometabolic Diseases

4.1 Type 2 Diabetes Mellitus

Oxidative stress and redox biomarkers Type 2 diabetes mellitus offers a conceptual framework on which the pathogenesis of diabetic complications is based on hyperglycaemia-induced ROS production. In Bigagli *et al.*, a review of the literature on circulating oxidative stress biomarkers in T2DM clinical studies presented results of consistent increases in lipid peroxidation products, protein carbonyls, and advanced glycation end products and a decrease in antioxidant capacity [4]. The clinical usefulness of oxidative-stress biomarkers in T2DM can be developed to multiple uses. Robson *et al.*, assessed the value of biomarker panel in the risk assessment of cardiovascular disease in patients with T2DM and confirmed that combination analysis of biomarkers is better at cardiovascular events prediction compared to individual markers [10]. The use of oxidative-stress markers in combination with the conventional cardiovascular risk factors as well as the glycaemic control measures enhances risk classification and can guide the process of the prevention strategy intensification [1, 4, 10]. Xuan *et al.*, conducted a pooled analysis of two cohort studies on the relationship between serum oxidative-stress markers and the occurrence of major cardiovascular events, cancer, and all-cause mortality in patients with T2DM [9]. This mass study suggested oxidative-stress biomarkers as independent predictors of poor outcomes over and above traditional risk factors, which means that they may be useful in clinical decision-making

[9]. However, the research also emphasised the need to have standardised measurement procedures and validation in populations that were heterogeneous [9].

4.2 Cardiovascular Disease

Cardiovascular disease is a non-homogenous group of diseases, including coronary artery disease, heart failure, and peripheral vascular disease, which is combined by a common shared pathogenic factor, oxidative stress. Daiber *et al.*, provide an in-depth overview of redox-related biomarkers in human cardiovascular disease, including both traditional indices and other methods going beyond the traditional biomarkers [12]. The review highlights the complexity of redox signalling in cardiovascular pathophysiology, in which the more complex aspects of spatial and temporal dynamics of ROS generation and elimination might be insufficiently revealed using more traditional measures of overall oxidative stress [12]. More sophisticated biomarkers, such as the quantification of certain species of ROS, redox-sensitive protein modifications, and compartment-specific markers of oxidative damage would be more informative regarding the mechanism but their common use in clinical practice is limited by practical considerations [12]. A key predictor of cardiovascular events is arterial stiffness which has strong links with both oxidative and nitrosative stress. The study by Mozos and Luca of the two-way interaction between oxidative stress, nitrosative stress, and vascular stiffness revealed that oxidative damage enhances the vascular stiffening process and that the enhancement of oxidative stress of increased arterial stiffness, due to haemodynamic perturbations [21]. Such a reciprocal correlation implies that redox biomarkers may be used as a surrogate endpoint of vascular ageing and subclinical cardiovascular disease [21].

4.3 Metabolic Syndrome

A combination of abdominal obesity, insulin resistance, dyslipidaemia, and hypertension are known as metabolic syndrome, thus forming high-risk profile of cardiovascular disease and type 2 diabetes. Oxidative stress also acts as a mechanistic rational connection between the separate elements of metabolic syndrome [14, 22]. A systematic review of oxidative stress biomarkers in patients with metabolic syndrome and other related conditions, Vona *et al.*, observed similar increases in ROS production and lipid peroxidation and reduced antioxidant capacity in the target populations [14]. The review has shown the potential future use of oxidative stress biomarkers to screen high-risk patients before overt disease onset and in patient response to lifestyle changes and pharmacological measures [14]. The study by Šebeková *et al.*, is a cross-sectional study that measured the relationship between inflammatory and oxidative status indicators and the elements of the metabolic syndrome in 40-to 45-year-old women [13]. The results showed that the indicators of oxidative stress were related to the count of metabolic syndrome elements, and the correlation was strong to abdominal obesity and insulin resistance [9]. These findings substantiate the assumption that oxidative stress measurement could be useful in enhancing early diagnosis and risk classification in metabolic syndrome [9]. To measure the joint effect of oxidative stress, inflammation, and dyslipidaemia in people with a range of glucose control, Klisic, used principal component analysis [8]. Multivariate analysis revealed that

clear patterns of biomarkers exist between normal glucose tolerance, prediabetes, and diabetes, indicating that oxidative stress biomarkers have the potential to determine those in transitional disease phases who might be subjected to more vigorous prevention efforts [18].

4.4 Hypertension and Vascular Dysfunction

Oxidative stress is closely connected with hypertension and vascular dysfunction via several mechanisms, which are the dysfunction of endothelium, the proliferation of vascular smooth muscle cells, and arterial remodelling [21, 23]. Charlton *et al.*, examined the presence of oxidative stress and inflammation in the renal and cardiovascular complications of diabetes with a special focus on the role of oxidative damage in diabetic nephropathy and hypertensive kidney disease [23]. Their information shows that oxidative stress biomarkers are associated with blood pressure measurements, albuminuria, and progressive renal dysfunction in diabetic patients, which means that they can be used to control the progression of the disease and make therapeutic choices [23]. Ndisang *et al.*, provided a more general view of the overlap between oxidative stress and inflammation between obesity, diabetes, hypertension, and associated cardiometabolic comorbidities with regards to common pathogenic pathways and future therapeutic opportunities [24].

5. Sex-Specific and Population-Based Considerations

The recent evidence suggests that sex-specific differences have significant effects on the performance of oxidative stress biomarkers and the disease relationships. Bourgonje *et al.*, also found that protein-adjusted R-SH and homocysteine were differentiated biomarker patterns between men and women in the PREVENT study; in men, these biomarkers were predictors of cardiovascular events, whereas bilirubin was a stronger predictor of mortality in women [2]. These sex-specific differences can be the evidence of the hormonal regulation of redox homeostasis, where estrogen has antioxidant effects and regulates the production of ROS [2]. The clinical implications are also substantial and the implication is that sex stratified reference ranges and risk prediction models may help to augment the applicability of biomarkers [2]. Population-based studies also show that there is also a variation in oxidative stress biomarkers according to age cohorts, ethnic groups, and regions of the world, and therefore there is a requirement of population-specific validation research [9, 14].

6. Integration with Inflammatory Biomarkers

Oxidative stress and inflammation are closely linked together in a network, in which ROS stimulate inflammatory signalling cascades and inflammatory mediators promote oxidative damage. Redox biomarkers in combination with inflammatory biomarkers provide more comprehensive understanding of disease pathophysiology, as well as better risk stratification [6, 7, 13]. Lopez-Armas *et al.*, considered the synergistic value of circulating microRNAs (c-miR-21, c-miR-126), redox status, and inflammatory state as predictors of vascular injury in patients with type 2 diabetes and showed that microRNA signatures with oxidative and inflammatory status were significantly more accurate to predict diabetic vascular complications than traditional risk factors [6]. This multidimensional strategy explains the interrelation of the redox dysregulation and the

inflammatory activation in the development of the cardiometabolic diseases [6]. Quetglas-Llabrés *et al.*, evaluated the status of inflammatory and oxidative stress markers according to the adherence to the Mediterranean diet in patients with metabolic syndrome and found that adherence to the Mediterranean diet was associated with less oxidative damage and inflammation [7]. These results propose the use of lifestyle factors in an integrated approach to assessing and managing risks [7]. Sun *et al.*, discussed the two-way interaction between inflammation and oxidative stress in metabolic and cardiovascular diseases and highlighted that oxidative stress triggers inflammatory responses, and inflammation also maintains oxidative injuries [27]. This mechanistic model favors the clinical usefulness of combined biomarker panels which measure both the oxidative and inflammatory aspects of cardiometabolic disease [27].

7. Genetic Determinants of Redox Status

Genetic variation at genes of antioxidant enzymes, redox sensitive transcription factors and ROS inducing enzyme regulate individual predisposition to oxidative stress and cardiometabolic illnesses. Zazueta *et al.*, gave a comprehensive overview of genetic variants that control redox homeostasis with special focus on the transcription factor, Nrf2, in the cardiometabolic scenarios [25]. Oxidative stress activates the expression of many cytoprotective genes through the action of Nrf2; single nucleotide polymorphisms (SNPs) in the NFE2L2 gene (encoding Nrf2) and a Nrf2 regulatory partner KEAP1 regulate Nrf2 activity and antioxidant potential [25]. These genetic variations have been linked to varying predisposition to diabetes, cardiovascular disease and metabolic syndrome, thus providing possible opportunities of individualized risk evaluation and directed interventions [25]. SOD3, which codes extracellular superoxide dismutase, has functional polymorphisms which affect cardiovascular outcomes and enzyme activity. Mohammadi *et al.*, showed that the allelic variations of SOD3 predict the risk of myocardial infarction and mortality in diabetic subjects, and that the interactions between genes and the environment alter the relationships [3]. Combining genetic data with measurements of biochemical biomarkers can contribute to the further stratification of risk and to the determination of individuals who are the most likely to respond to an antioxidant-based treatment [3, 25].

8. Therapeutic Implications and Interventions

Oxidative stress emergence as a key pathogenic mediator of cardiometabolic diseases has prompted a surge of research on the application of antioxidant-based therapeutic interventions. However, the clinical trials of antioxidant supplementation have not produced good results with only a few showing provable cardiovascular effects [19, 20]. Donia *et al.*, provided an overview of the oxidative stress and inflammatory treatment in cardiovascular disease with a mechanistic basis and translational issues of antioxidant therapies [26]. The review provided the conclusion that the rudimentary antioxidant supplementation could not be adequate to counteract the multifactor character of oxidative stress in established disease [20]. Further specific interventions, such as the activation of endogenous antioxidant pathways by Nrf2 activation or the inhibition of particular enzymes that generate ROS could be more therapeutically active [20, 25]. The high-intensity interval

training was found to be a kind of redox medicine by Reljic, as the exercise-based oxidative stress was shown to induce adaptive antioxidant mechanisms and to restore the redox balance in heart-metabolic populations [15]. Controlled oxidative challenge leading to the induction of adaptations beneficial to the organism is known as hormetic, as opposed to the direct administration of antioxidants and is consistent with physiologic principles of therapeutic approaches [15]. Reviewing the natural polyphenols in metabolic syndrome, Zhang *et al.*, investigated the protective effects and clinical use [19]. Polyphenols reduce oxidative stress by direct ROS scavenging, metal chelation and endogenous antioxidants pathway activation [19]. The clinical evidence suggests that diets containing polyphenols and supplements enhance the biomarkers of oxidative stress and metabolism, but the long-term cardiovascular outcomes are not widely available [19]. Singh *et al.*, examined the impact of molecular hydrogen on the cardiovascular and metabolic diseases pathophysiology and management [20]. Molecular hydrogen is a selective antioxidant, which neutralises highly reactive hydroxyl radicals whilst maintaining physiological ROS signalling [20]. Clinical trials on the initial phases indicate a possible improvement in the outcome in cardiovascular and metabolic, although larger randomized trials are needed to establish efficacy [20].

9. Methodological Challenges and Standardization

Irrespective of significant progress in the study of oxidative stress biomarkers, there are significant barriers to clinical translation due to severe methodological issues. According to Baldassarre *et al.*, systematic biomarker selection, validation, and standardization in cardiovascular research of type 2 diabetes is critically needed [1]. The major challenges include pre-analytical variability (sample collection, processing, and storage), analytical variability (measurement techniques and calibration), and biological variability (diurnal rhythms, dietary effects and acute stress reactions) [1]. Robberecht *et al.*, investigated the biomarkers of metabolic syndrome both biochemically and in clinical terms, and pointed out the necessity of a standardized range of reference and quality-control measures [18]. Lack of international reference methods on most of the oxidative stress biomarkers makes cross-study comparison challenging and facilitation of clinical application difficult [18]. Global programs and projects towards establishing standard protocols and reference materials are vital to the growth of the field [1, 18]. The interpretation of the oxidative stress biomarkers requires the consideration of confounding factors such as age, sex, smoking, medication, and comorbidities [1, 2]. The multivariate statistical approaches and machine learning algorithms could help to decouple those non-linear relationships and improve the performance of biomarkers in heterogeneous clinical groups [18].

10. Future Directions and Research Gaps

There are various research gaps that are critical and need to be addressed in order to gain more clinical utility of redox biomarkers in cardiometabolic medicine. To determine the independent predictive value of redox biomarkers beyond conventional risk factors, first, the large-scale prospective studies including the standardized measurement of the biomarkers and the long-term clinical outcome are needed [9, 10]. These studies must also cover a wide range of populations to be generalized and that they can also

determine the pattern of biomarkers within the population [2]. Second, point-of-care testing platforms of bioindicators of oxidative stress would be developed and allow clinical use and real-time redox status monitoring [1]. Existing laboratory-based tests often require both special equipment and skills, which restricts their availability in a typical clinical practice [11]. Future innovation in biosensor technology and microfluidic devices can allow the measurement of oxidative stress during the point of care in a rapid, cost-effective manner [12]. Third, redox biomarkers will be potentially integrated with other omics technologies (genomics, transcriptomics, proteomics and metabolomics) to have a complete molecular phenotyping and personalized risk assessment [25]. Novel therapeutic targets and combinations of biomarkers may be revealed in systems biology approaches that model the complex interactions between oxidative stress, inflammation, metabolism and genetics [8, 16]. Fourth, it is urgently required that the intervention studies are conducted to examine whether oxidative-stress biomarker-guided therapy is beneficial in improving clinical outcomes [15, 19, 20]. This would help to test the hypothesis that individually-focused antioxidant interventions, i.e. those that are specifically required to individuals with a history of oxidative stress, have better benefits than population-wide approaches to supplementation [19, 20]. Lastly, mechanistic research that provides causal links between particular redox biomarkers and disease outcomes will be used to drive therapeutic development and interpolate biomarkers [12, 16]. Higher-order experimental tools such as the human-derived organoids and precision-cut tissue slices can be used to fill the gap between in-vitro cell culture research and clinical research [16].

11. Conclusion

Redox biomarkers and oxidative stress have become central to the definition of pathophysiology of cardiometabolic and inflammatory diseases and the improvement of clinical risk evaluation and post-treatment monitoring. The existing literature shows that biomarkers like protein-adjusted free thiols, homocysteine, lipid peroxidation products and antioxidant enzyme activities have independent prognostic value of cardiovascular events and death especially when combined with other inflammatory indicators and genetic determinants. However, there are still considerable issues related to the standardization of analytical methods, the development of population-specific reference ranges, and the ability to prove that biomarker-based interventions can enhance clinical outcomes. The subject is moving out of crude methods of measuring overall oxidative stress to more complex methods of measuring specific ROS species, compartment-specific oxidative damage, and redox signaling dynamics. The combination of redox biomarkers and multi-omics and systems biology modeling is promising in the development of personalized medicine in cardiometabolic disease. The future of biomarker research ought to focus on big-scale prospective validation, creation of point-of-care testing systems, mechanistic research of biomarker-disease interactions, and randomized trials of biomarker-guided treatment regimens. Further methodological development and clinical validation on whether redox biomarkers will revolutionize cardiometabolic and inflammatory disease prevention, diagnosis and treatment will be determined.

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