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Serum Lipid Profile and Oxidative Stress Markers in Patients With Type 2 Diabetes Mellitus

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ABSTRACT

Type 2 diabetes mellitus is usually described through glucose, yet two other biochemical stories run alongside it: a characteristic disturbance of the serum lipid profile and a state of heightened oxidative stress. This narrative review asks how these two stories are connected and how much the published literature can support. It draws on work on diabetic dyslipidaemia, on the chemistry and measurement of oxidative stress markers, and on trials of lipid-lowering and antioxidant interventions published up to 2013, and it reports no new data. The usual lipid picture combines raised triglycerides, low high-density lipoprotein cholesterol and small, dense low-density lipoprotein particles that a standard LDL cholesterol value can understate. Oxidative stress in the same patients is often inferred from malondialdehyde-type assays, isoprostanes, protein carbonyls and measures of antioxidant capacity, but these markers differ in specificity and many are sensitive to how blood is handled. Evidence that the two disturbances reinforce each other is biologically coherent and largely observational. Statins have a firm evidence base in diabetes, fibrates a weaker one, and antioxidant vitamins have not delivered the benefit that the oxidative hypothesis predicted. The review concludes that lipid measurement should be read together with particle-level information, that oxidative markers need method-aware interpretation, and that causal claims remain unproven.

Keywords: Type 2 diabetes mellitus; Serum lipid profile; Diabetic dyslipidaemia; Oxidative stress; Lipid peroxidation; Antioxidants; Narrative review

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Article Class: Narrative Review

1. Introduction

Type 2 diabetes mellitus is usually described through glucose, but a patient's blood carries at least two other stories. One is a recognisable change in the serum lipid

profile. The other is a state of heightened oxidative stress, in which reactive oxygen species and their products appear to outrun the body's defences. Both have been linked to the vascular complications that



dominate the long-term burden of the disease (1, 2). Mortality from vascular disease is higher among people with diabetes, and the excess is not explained by glucose alone (3, 4).

The two stories are often told together, because lipoproteins are a favourite target of oxidation and oxidised lipoproteins are a favourite suspect in atherosclerosis (5, 6). In practice, though, the evidence for each is gathered by different methods, in different laboratories, with different degrees of rigour. A routine lipid panel is standardised and cheap; a measure of oxidative stress is neither, and the choice among the many available markers is far from neutral (7, 8).

This review therefore asks a practical question. What does the published literature say about how the serum lipid profile and markers of oxidative stress behave in type 2 diabetes, how reliably can those markers be measured, and what do interventional studies tell us about whether the connection is causal? It reports no data of its own and no local cohort; where the title might suggest a specific population, we mean the published literature in general. The aim is a fair account of what is known and what is only repeated.

2. Literature Review

2.1 The Lipid Profile in Type 2 Diabetes

The classic pattern, often called diabetic dyslipidaemia, combines raised triglycerides, lowered high-density lipoprotein (HDL) cholesterol and a predominance of small, dense low-density lipoprotein (LDL) particles (9, 10). Table 1 sets out the usual features and the mechanisms most often proposed. The striking point is that LDL cholesterol itself is frequently unremarkable. A patient may have an LDL cholesterol value close to that of a person without diabetes and still carry a larger number of atherogenic

particles (10, 11).

The central mechanism is a liver that is, in effect, over-instructed. When insulin signalling is impaired, fatty acids arrive from adipose tissue in excess, hepatic production of very-low-density lipoprotein (VLDL) rises, and clearance of triglyceride-rich particles slows (2, 12). Once triglyceride-rich particles are abundant, lipid exchange among lipoproteins remodels HDL and LDL, leaving HDL smaller and cleared faster and LDL smaller and denser (2, 9). Small shifts of this kind may look trivial in one patient and still matter across years.

Table 1. Usual features of the serum lipid profile in type 2 diabetes.

Feature	Usual direction	Mechanism emphasised
Triglycerides	Raised	Hepatic VLDL overproduction, slow clearance (9, 12)
HDL cholesterol	Lowered	Exchange of lipids with triglyceride-rich particles (2)
LDL cholesterol	Often near usual	Concentration may hide particle changes (10)
LDL particles	Smaller, denser	Longer residence, easier oxidation (5, 10)
Apolipoprotein B	Relatively high	Counts atherogenic particles (11)
After-meal lipaemia	Prolonged	Delayed removal of remnants (2)

Note: Qualitative summary of directions described in the cited reviews; magnitudes vary between populations and are not given.

2.2 How Oxidative Stress Arises in Diabetes

Several routes lead from a diabetic metabolic state to oxidative stress. A well-known unifying proposal holds that high glucose drives excess superoxide production by the mitochondrial electron transport chain, which in turn activates a set of damaging pathways in vascular cells



(1, 13). Older work had already shown that glucose can autoxidise and modify proteins in the process (14), and reviews through the 1990s and 2000s described a state in which free radical production rises while antioxidant defences are, at best, no better (15, 16).

An important qualification came from those who looked at the chemistry more closely. Baynes and Thorpe argued that much of the damage seen in diabetes reflects altered carbohydrate and lipid chemistry, and so the burden of modified molecules cannot be read as a simple measure of radical production (17). In other words, an elevated marker may mean more oxidant, less clearance or more modifiable substrate, and the marker alone cannot say which. This is one reason the same marker can look decisive in one report and unremarkable in the next.

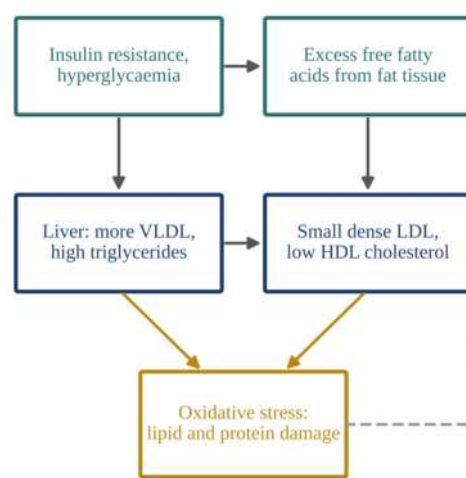
Oxidative stress is also linked to insulin resistance itself, not only to its consequences. Reactive oxygen species have been proposed as a unifying element in the stress-activated signalling that impairs insulin action and beta-cell function (18, 19). The beta cell appears to be unusually vulnerable because of its modest antioxidant enzyme defences, and chronic exposure to high glucose and to fatty acids is thought to damage it further (20). In humans, greater adiposity is accompanied by greater systemic oxidative stress, which supports the idea that the two travel together (21).

2.3 Where Lipids and Oxidation Meet

The meeting point is the lipoprotein particle. Oxidatively modified LDL is taken up by macrophages in an unregulated way, forming foam cells, and the oxidation hypothesis of atherosclerosis grew out of this observation (5, 6). In diabetes the ingredients for oxidation are plentiful: LDL that is small and dense, an environment rich in reactive species and,

in the circulation, glycated or otherwise modified proteins (10, 22). Aldehydes such as malondialdehyde and 4-hydroxynonenal, formed when polyunsaturated lipids break down, can in turn modify proteins and propagate the damage (23).

Figure 1 sketches how these strands may reinforce one another. We stress the word *may*. The drawing is a hypothesis in diagram form, and the dashed route back to insulin signalling is the least settled link. The arrow from oxidative stress to insulin resistance rests on mechanistic and animal work (18, 19), whereas the arrows from insulin resistance to dyslipidaemia are better supported by human metabolic studies (9, 12). Reviews of this kind are more useful when they say where the evidence stops than when they smooth it over.



feedback to insulin signalling (dashed route, hypothesis)

Figure 1. How hyperglycaemia, excess fatty acids and lipoprotein change may feed one another (schematic, not data).

2.4 Measuring Oxidative Stress

Measurement is where much of the disagreement begins. The thiobarbituric acid reaction, introduced for tissue lipid peroxides in 1979 (24), remains popular because it is simple, but it reacts with many substances besides malondialdehyde,



and reviews of malondialdehyde as a biomarker repeatedly warn about this lack of specificity (25).

F2-isoprostanes are more specific. These prostaglandin-like compounds form in vivo through free-radical catalysed oxidation of arachidonic acid, independent of cyclooxygenase (26), and they have been proposed as among the most reliable indices of oxidative stress in vivo, provided sampling and assay are careful (27, 28). Studies in diabetes have reported higher isoprostane formation and a relation to metabolic control (22), though such assays are more demanding and less available in routine laboratories. Table 2 compares the main families of markers and the cautions that go with each.

Protein carbonyls provide a different window. They are relatively stable products of oxidative protein damage and are measured by well-established chemistry, but they arise from several oxidative routes and are not specific to any one source (29). Total antioxidant capacity assays, such as those based on ferric reducing ability or a decolourisation reaction, offer a convenient single number (30, 31), yet the number is a composite of many reducing substances, and its biological meaning is hard to state. A raised value may reflect uric acid, albumin or bilirubin as much as any dietary or enzymatic antioxidant. General reviews of biomarkers of oxidative damage and of the pitfalls of measuring reactive species conclude that no single marker is adequate, and that a combination of methods, honestly described, is preferable (7, 8). Interpretation is easier when the same sample set has been run for more than one marker family, because agreement between families is more persuasive than any single result. A clinician reading a biomarker paper needs to know what was actually measured, and how.

Table 2. Commonly used oxidative stress markers and their main cautions.

Marker	What it reflects	Main caution
TBARS or MDA	Lipid peroxidation products	Not specific; assay artefacts (24, 25)
F2-isoprostanes	Free-radical lipid oxidation	Needs careful sampling and assay (27, 28)
Oxidised LDL	Modified lipoprotein particles	Antibody and method dependent (5, 6)
Protein carbonyls	Oxidative protein damage	Stable but not source specific (29)
Total antioxidant capacity	Combined reducing power	Hard to link to biology (30, 31)
Antioxidant enzymes	Defence capacity	Tissue and serum differ (7)

Note: Cautions are those raised in the cited methodological literature, not findings from any single study.

The lipid side has its own measurement traps. LDL cholesterol is commonly calculated, not measured, using an equation that is known to become unreliable when triglycerides are high (32), which is precisely the situation in diabetic dyslipidaemia. Apolipoprotein B counts the atherogenic particles more directly and has been argued to be a better index of coronary risk and a better treatment target than the cholesterol values alone (11). Insulin resistance, often needed as a covariate in such studies, is itself usually estimated from fasting values through a model rather than measured directly (33).

3. Materials and Methods

3.1 Scope and Question

The review asks a single question in three parts, framed in advance of reading the literature. How do the serum lipid profile and markers of oxidative stress behave in type 2 diabetes in the published literature? How well can those markers be measured



and compared across studies? And what do interventional studies imply about whether the lipid and oxidative disturbances are causal contributors to vascular harm or merely companions of it? None of these choices is exotic, but each one shapes what the reader can conclude.

3.2 Literature Assembly

The review draws on peer-reviewed work in four areas: the physiology and clinical epidemiology of diabetic dyslipidaemia; the chemistry and measurement of oxidative stress markers; mechanistic work connecting oxidation, insulin resistance and lipoprotein biology; and randomised trials and meta-analyses of lipid-lowering and antioxidant interventions.

We did not run a formal systematic search and we do not claim one. This is a narrative synthesis, and the choice of sources reflects the authors' judgement. The practical consequence is that the review is a better guide to the shape of the argument than to the exact magnitude of any difference, and for that reason it avoids quoting numerical results from individual studies that could not be re-checked against their primary reports for this article.

3.3 Appraisal Framework

To judge how far a report can be trusted, we asked four short questions of each kind of study. Was the marker specific to the process claimed (7, 25)? Were fasting status, sample handling, storage time and storage temperature described? Were patients on lipid-lowering or antioxidant treatment, which would change the picture (34, 35)? And did the design allow a causal reading, or only an association, and was it large enough for the question? None of these checks is demanding, yet many reports leave them unanswered. Table 3 lists the interventions we considered and how we read them.

Table 3. Interventions that bear on the lipid and oxidative hypotheses.

Intervention	Main finding	Reading
Statins	Fewer vascular events in diabetes (34, 36, 37)	Firm evidence
Fenofibrate	Mixed: little on primary outcome (38, 39)	Possible subgroup role
Vitamin E, C, carotene	No clear vascular benefit (35, 40)	Hypothesis not supported
Antioxidant supplements, pooled	Possible harm signal (41)	Caution
Antioxidants with exercise	Blunted insulin sensitisation (42)	Redox signal may help

Note: Findings are stated qualitatively as reported in the cited trials and meta-analyses.

4. Results

4.1 What the Observational Literature Shows

Across reviews, the descriptive findings are consistent in direction. Triglycerides are raised, HDL cholesterol is lowered and LDL particles are smaller and denser (2, 10). Markers of lipid peroxidation, protein oxidation and oxidised LDL are, on the whole, reported as higher in people with diabetes than in those without, and the reports link them to poor glycaemic control and to complications (16, 22, 43). A systematic reading of that literature would be needed to say how strong the typical difference is, and we do not attempt to supply a figure, and the samples behind it are often small and heterogeneous (44). The difficulty is not that the numbers are wrong, only that they answer a narrower question than the title suggests.

4.2 Reading Lipids and Oxidative Markers Together

If oxidative stress contributes to lipoprotein damage, markers of the two should travel together, and in a loose way they do. Higher peroxidation markers tend to be reported alongside higher



triglycerides and lower HDL cholesterol (22, 43).

Several confounders deserve explicit mention. Adiposity raises both triglycerides and oxidative markers (21, 45), and so an association between the two may simply reflect body fat. Glycaemic control affects both as well (1, 22). And diet, smoking, physical activity and drug treatment alter oxidative markers independently of diabetes. Studies that adjust for these factors are in the minority, and an unadjusted correlation between a lipid value and an oxidative marker should be read with that in mind.

Pre-analytical handling affects the oxidative side more than the lipid side. Fasting state alters triglycerides and the particles that carry them, delayed separation of serum or plasma can change several markers, and storage and freeze–thaw cycles may alter peroxidation products and antioxidant measures (7, 8). A marker that is stable in the freezer may still have been disturbed before it got there.

	Lipid peroxides	Iso-prostanates	Protein carbonyls	Antioxidant capacity
Specificity	limited	better	moderate	limited
Sample stability	moderate	moderate	better	moderate
Routine use	better	limited	moderate	better
Link to risk	moderate	moderate	limited	limited

relative judgement from the literature; schematic, not data

Figure 2. Qualitative matrix of what common marker families can and cannot tell the reader (schematic, not data).

4.3 Interventions That Test the Hypotheses

Treatment trials give the strongest evidence on whether lipids matter. Statins reduce major vascular events in people with diabetes, and the proportional benefit

appears broadly similar to that in people without diabetes, as shown in a large meta-analysis and in dedicated diabetes trials (34, 36, 37). For the clinician this is the most secure result in the whole field, and it means that lipid management is not an optional extra in type 2 diabetes. Current standards of care reflect it (46).

The record for fibrates is more mixed. In a large trial of fenofibrate in type 2 diabetes the primary coronary outcome was not significantly reduced, although some secondary outcomes pointed towards benefit (38). A later trial that added fenofibrate to a statin did not reduce major cardiovascular events overall, though it suggested that people with high triglycerides and low HDL cholesterol might benefit (39). That suggestion was a subgroup observation and should be read as a hypothesis for further testing. Importantly, these are trials of lipid change, and they say little about oxidative stress. Read this way, a null result in a small study is not proof that nothing is there.

The oxidative hypothesis has been tested more directly, and it has fared worse. Large trials of antioxidant vitamins, including vitamin E, found no clear reduction in vascular events (35, 40), and a meta-analysis of randomised trials of antioxidant supplements raised the possibility that some preparations may even be harmful (41). A further study found that vitamin C and E supplementation blunted some of the metabolic benefits of exercise, which suggests that low-level oxidant signalling may be part of normal adaptation (42). Figure 2 and Table 3 should be read together with this result in mind.

These findings need careful interpretation. The failure of antioxidant vitamins does not show that oxidative stress is irrelevant; what the trials do show is that the simple



step from marker to treatment, antioxidant given because the marker is high, has not worked, and that the causal role of oxidative stress in human vascular disease remains open (17, 43). Figure 3 places the methods and trials discussed here on a single line. That is a modest claim, and it is the one the literature will currently bear.

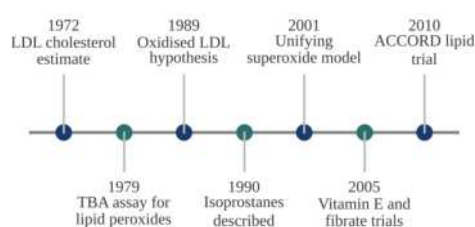


Figure 3. Timeline of landmark methods and trials discussed in this review (schematic; spacing is not to scale).

4.4 Putting the Evidence in Order

Read in that order, the literature supports only a measured statement. Lipid disturbance in type 2 diabetes is real, well characterised and treatable with benefit. Oxidative stress is repeatedly observed and mechanistically plausible, but its measurement is uneven and its causal role in clinical vascular disease has not been established by trials of antioxidants.

5. Discussion

5.1 Interpretation and Practical Reading

The main finding of this review is a layered one. At the bottom layer sits a well-characterised lipid disturbance that is amenable to treatment, with statins having the firmest support (34, 36). In the middle layer sit oxidative markers, whose direction of difference is consistent but whose meaning depends on the method and the sample (7, 8). At the top layer sit causal claims linking the two, which are

coherent and largely untested in humans (19, 43). Nothing in this reading argues against measuring these markers; it argues for saying what they can and cannot show.

For laboratory practice, this has modest but concrete implications. A lipid panel in a patient with diabetes should be read with attention to triglycerides and HDL cholesterol and, where available, to apolipoprotein B, since LDL cholesterol may understate particle burden (10, 11). For oxidative markers, a report should state which marker was used and why, because a thiobarbituric acid result and an isoprostane result answer different questions (25, 27). These cautions apply with equal force to many other biomarkers, not only to those discussed here.

5.2 Limitations

This is a narrative review and shares the limitations of that form. The selection of sources reflects judgement, no formal search or quality scoring was done, and the review does not quote numerical results from individual studies. A reader who needs an effect size should consult the original reports directly, applying the appraisal questions above. The review is also limited to literature available to 2013, and later developments in lipid-lowering therapy and in redox biology are outside its scope.

5.3 Directions for Future Work

Three needs stand out. First, studies that measure oxidative stress with specific markers such as isoprostanes, under standardised sampling, in well-described patients (11, 27). Second, longitudinal designs that show whether oxidative changes precede or follow lipid changes. Third, interventions that target oxidative pathways more specifically than blanket vitamin supplementation (13, 42). Until then, claims that one disturbance drives the other are hypotheses.



6. Conclusion

The serum lipid profile in type 2 diabetes is well described: raised triglycerides, lowered HDL cholesterol and small, dense LDL particles that routine LDL cholesterol can understate. Oxidative stress markers are generally reported as higher in the same patients, and a biologically coherent account links the two through lipoprotein modification. The evidence for the lipid side, including treatment benefit, is stronger than the evidence for the oxidative side, where markers are method dependent and antioxidant trials have not delivered. The sensible reading is therefore a careful one, in which lipid findings are interpreted with particle information in mind and oxidative markers are reported with their limits.

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9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

G.K. conceived the review and wrote the sections on oxidative stress chemistry. T.M. wrote the sections on lipid metabolism and clinical interpretation. L.L. wrote the sections on measurement and interventional evidence. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No patients or animals were studied and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

13. References

1. Brownlee, M. (2001). Biochemistry and molecular cell biology of diabetic complications. *Nature*, 414(6865), 813–820. DOI: [10.1038/414813a](https://doi.org/10.1038/414813a)
2. Taskinen, M.-R. (2003). Diabetic dyslipidaemia: From basic research to clinical practice. *Diabetologia*, 46(6), 733–749. DOI: [10.1007/s00125-003-1111-y](https://doi.org/10.1007/s00125-003-1111-y)
3. Emerging Risk Factors Collaboration. (2010). Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. *The Lancet*, 375(9733), 2215–2222. DOI: [10.1016/S0140-6736\(10\)60484-9](https://doi.org/10.1016/S0140-6736(10)60484-9)
4. Haffner, S. M., Lehto, S., Rönkä, T., Pyörälä, K., & Laakso, M. (1998). Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *New England Journal of Medicine*, 339(4), 229–234. DOI: [10.1056/NEJM199807233390404](https://doi.org/10.1056/NEJM199807233390404)
5. Steinberg, D., Parthasarathy, S., Carew, T. E., Khoo, J. C., & Witztum, J. L. (1989). Beyond cholesterol: Modifications of low-density lipoprotein that increase its atherogenicity. *New England Journal of Medicine*, 320(14), 915–924. DOI: [10.1056/NEJM198904063201407](https://doi.org/10.1056/NEJM198904063201407)
6. Witztum, J. L., & Steinberg, D. (1991). Role of oxidized low density lipoprotein in atherogenesis. *Journal of Clinical Investigation*, 88(6), 1785–1792. DOI: [10.1172/JCI115499](https://doi.org/10.1172/JCI115499)
7. Halliwell, B., & Whiteman, M. (2004). Measuring reactive species and oxidative damage in vivo and in cell culture: How should you do it and what do the results mean? *British Journal of Pharmacology*, 142(2), 231–255. DOI: [10.1038/sj.bjp.0705776](https://doi.org/10.1038/sj.bjp.0705776)
8. Dalle-Donne, I., Rossi, R., Colombo, R., Giustarini, D., & Milzani, A. (2006). Biomarkers of oxidative damage in human disease. *Clinical Chemistry*, 52(4), 601–623. DOI: [10.1373/clinchem.2005.061408](https://doi.org/10.1373/clinchem.2005.061408)
9. Goldberg, I. J. (2001). Diabetic dyslipidemia: Causes and consequences. *Journal of Clinical Endocrinology & Metabolism*, 86(3), 965–971. DOI: [10.1210/jcem.86.3.7304](https://doi.org/10.1210/jcem.86.3.7304)
10. Krauss, R. M. (2004). Lipids and lipoproteins in patients with type 2 diabetes. *Diabetes Care*, 27(6), 1496–1504. DOI: [10.2337/diacare.27.6.1496](https://doi.org/10.2337/diacare.27.6.1496)
11. Sniderman, A. D., Furberg, C. D., Keech, A., Roeters van Lennep, J. E., Frohlich, J., Jungner,



- I., & Walldius, G. (2003). Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. *The Lancet*, 361(9359), 777–780. DOI: [10.1016/S0140-6736\(03\)12663-3](https://doi.org/10.1016/S0140-6736(03)12663-3)
12. Adiels, M., Olofsson, S.-O., Taskinen, M.-R., & Borén, J. (2008). Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 28(7), 1225–1236. DOI: [10.1161/ATVBAHA.107.160192](https://doi.org/10.1161/ATVBAHA.107.160192)
13. Giacco, F., & Brownlee, M. (2010). Oxidative stress and diabetic complications. *Circulation Research*, 107(9), 1058–1070. DOI: [10.1161/CIRCRESAHA.110.223545](https://doi.org/10.1161/CIRCRESAHA.110.223545)
14. Wolff, S. P., & Dean, R. T. (1987). Glucose autooxidation and protein modification: The potential role of “autooxidative glycosylation” in diabetes. *Biochemical Journal*, 245(1), 243–250. DOI: [10.1042/bj2450243](https://doi.org/10.1042/bj2450243)
15. Baynes, J. W. (1991). Role of oxidative stress in development of complications in diabetes. *Diabetes*, 40(4), 405–412. DOI: [10.2337/diab.40.4.405](https://doi.org/10.2337/diab.40.4.405)
16. Maritim, A. C., Sanders, R. A., & Watkins, J. B. (2003). Diabetes, oxidative stress, and antioxidants: A review. *Journal of Biochemical and Molecular Toxicology*, 17(1), 24–38. DOI: [10.1002/jbt.10058](https://doi.org/10.1002/jbt.10058)
17. Baynes, J. W., & Thorpe, S. R. (1999). Role of oxidative stress in diabetic complications: A new perspective on an old paradigm. *Diabetes*, 48(1), 1–9. DOI: [10.2337/diabetes.48.1.1](https://doi.org/10.2337/diabetes.48.1.1)
18. Evans, J. L., Goldfine, I. D., Maddux, B. A., & Grodsky, G. M. (2002). Oxidative stress and stress-activated signaling pathways: A unifying hypothesis of type 2 diabetes. *Endocrine Reviews*, 23(5), 599–622. DOI: [10.1210/er.2001-0039](https://doi.org/10.1210/er.2001-0039)
19. Houstis, N., Rosen, E. D., & Lander, E. S. (2006). Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature*, 440(7086), 944–948. DOI: [10.1038/nature04634](https://doi.org/10.1038/nature04634)
20. Robertson, R. P., Harmon, J., Tran, P. O. T., & Poitout, V. (2004). Beta-cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. *Diabetes*, 53(Suppl. 1), S119–S124. DOI: [10.2337/diabetes.53.2007.S119](https://doi.org/10.2337/diabetes.53.2007.S119)
21. Furukawa, S., Fujita, T., Shimabukuro, M., Iwaki, M., Yamada, Y., Nakajima, Y., ... Shimomura, I. (2004). Increased oxidative stress in obesity and its impact on metabolic syndrome. *Journal of Clinical Investigation*, 114(12), 1752–1761. DOI: [10.1172/JCI21625](https://doi.org/10.1172/JCI21625)
22. Davì, G., Falco, A., & Patrono, C. (2005). Lipid peroxidation in diabetes mellitus. *Antioxidants & Redox Signaling*, 7(1–2), 256–268. DOI: [10.1089/ars.2005.7.256](https://doi.org/10.1089/ars.2005.7.256)
23. Esterbauer, H., Schaur, R. J., & Zollner, H. (1991). Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. *Free Radical Biology and Medicine*, 11(1), 81–128. DOI: [10.1016/0891-5849\(91\)90192-6](https://doi.org/10.1016/0891-5849(91)90192-6)
24. Ohkawa, H., Ohishi, N., & Yagi, K. (1979). Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Analytical Biochemistry*, 95(2), 351–358. DOI: [10.1016/0003-2697\(79\)90738-3](https://doi.org/10.1016/0003-2697(79)90738-3)
25. Del Rio, D., Stewart, A. J., & Pellegrini, N. (2005). A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. *Nutrition, Metabolism and Cardiovascular Diseases*, 15(4), 316–328. DOI: [10.1016/j.numecd.2005.05.003](https://doi.org/10.1016/j.numecd.2005.05.003)
26. Morrow, J. D., Hill, K. E., Burk, R. F., Nammour, T. M., Badr, K. F., & Roberts, L. J. (1990). A series of prostaglandin F₂-like compounds are produced in vivo in humans by a non-cyclooxygenase, free radical-catalyzed mechanism. *Proceedings of the National Academy of Sciences*, 87(23), 9383–9387. DOI: [10.1073/pnas.87.23.9383](https://doi.org/10.1073/pnas.87.23.9383)
27. Roberts, L. J., & Morrow, J. D. (2000). Measurement of F₂-isoprostanes as an index of oxidative stress in vivo. *Free Radical Biology and Medicine*, 28(4), 505–513. DOI: [10.1016/S0891-5849\(99\)00264-6](https://doi.org/10.1016/S0891-5849(99)00264-6)
28. Montuschi, P., Barnes, P. J., & Roberts, L. J. (2004). Isoprostanes: Markers and mediators of oxidative stress. *The FASEB Journal*, 18(15), 1791–1800. DOI: [10.1096/fj.04-2330rev](https://doi.org/10.1096/fj.04-2330rev)
29. Dalle-Donne, I., Giustarini, D., Colombo, R., Rossi, R., & Milzani, A. (2003). Protein carbonylation in human diseases. *Trends in Molecular Medicine*, 9(4), 169–176. DOI: [10.1016/S1471-4914\(03\)00031-5](https://doi.org/10.1016/S1471-4914(03)00031-5)
30. Erel, O. (2004). A novel automated direct measurement method for total antioxidant capacity using a new generation, more stable ABTS radical cation. *Clinical Biochemistry*, 37(4), 277–285. DOI: [10.1016/j.clinbiochem.2003.11.015](https://doi.org/10.1016/j.clinbiochem.2003.11.015)
31. Benzie, I. F. F., & Strain, J. J. (1996). The ferric reducing ability of plasma (FRAP) as a measure of “antioxidant power”: The FRAP assay. *Analytical Biochemistry*, 239(1), 70–76. DOI: [10.1006/abio.1996.0292](https://doi.org/10.1006/abio.1996.0292)
32. Friedewald, W. T., Levy, R. I., & Fredrickson, D. S. (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical Chemistry*, 18(6), 499–502. DOI: [10.1093/clinchem/18.6.499](https://doi.org/10.1093/clinchem/18.6.499)
33. Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C.



- (1985). Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, 28(7), 412–419. DOI: [10.1007/BF00280883](https://doi.org/10.1007/BF00280883)
34. Cholesterol Treatment Trialists' (CTT) Collaborators. (2008). Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: A meta-analysis. *The Lancet*, 371(9607), 117–125. DOI: [10.1016/S0140-6736\(08\)60104-X](https://doi.org/10.1016/S0140-6736(08)60104-X)
35. Heart Protection Study Collaborative Group. (2002). MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: A randomised placebo-controlled trial. *The Lancet*, 360(9326), 23–33. DOI: [10.1016/S0140-6736\(02\)09328-5](https://doi.org/10.1016/S0140-6736(02)09328-5)
36. Heart Protection Study Collaborative Group. (2003). MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: A randomised placebo-controlled trial. *The Lancet*, 361(9374), 2005–2016. DOI: [10.1016/S0140-6736\(03\)13636-7](https://doi.org/10.1016/S0140-6736(03)13636-7)
37. Colhoun, H. M., Betteridge, D. J., Durrington, P. N., Hitman, G. A., Neil, H. A. W., Livingstone, S. J., ... CARDS investigators. (2004). Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. *The Lancet*, 364(9435), 685–696. DOI: [10.1016/S0140-6736\(04\)16895-5](https://doi.org/10.1016/S0140-6736(04)16895-5)
38. Keech, A., Simes, R. J., Barter, P., Best, J., Scott, R., Taskinen, M.-R., ... FIELD study investigators. (2005). Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. *The Lancet*, 366(9500), 1849–1861. DOI: [10.1016/S0140-6736\(05\)67667-2](https://doi.org/10.1016/S0140-6736(05)67667-2)
39. ACCORD Study Group. (2010). Effects of combination lipid therapy in type 2 diabetes mellitus. *New England Journal of Medicine*, 362(17), 1563–1574. DOI: [10.1056/NEJMoa1001282](https://doi.org/10.1056/NEJMoa1001282)
40. Lonn, E., Bosch, J., Yusuf, S., Sheridan, P., Pogue, J., Arnold, J. M., ... HOPE and HOPE-TOO Trial Investigators. (2005). Effects of long-term vitamin E supplementation on cardiovascular events and cancer: A randomized controlled trial. *JAMA*, 293(11), 1338–1347. DOI: [10.1001/jama.293.11.1338](https://doi.org/10.1001/jama.293.11.1338)
41. Bjelakovic, G., Nikolova, D., Gluud, L. L., Simonetti, R. G., & Gluud, C. (2007). Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: Systematic review and meta-analysis. *JAMA*, 297(8), 842–857. DOI: [10.1001/jama.297.8.842](https://doi.org/10.1001/jama.297.8.842)
42. Ristow, M., Zarse, K., Oberbach, A., Klötting, N., Birringer, M., Kiehntopf, M., ... Blüher, M. (2009). Antioxidants prevent health-promoting effects of physical exercise in humans. *Proceedings of the National Academy of Sciences*, 106(21), 8665–8670. DOI: [10.1073/pnas.0903485106](https://doi.org/10.1073/pnas.0903485106)
43. Ceriello, A., & Motz, E. (2004). Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 24(5), 816–823. DOI: [10.1161/01.ATV.0000122852.22604.78](https://doi.org/10.1161/01.ATV.0000122852.22604.78)
44. Turner, R. C., Millns, H., Neil, H. A. W., Stratton, I. M., Manley, S. E., Matthews, D. R., & Holman, R. R. (1998). Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS 23). *BMJ*, 316(7134), 823–828. DOI: [10.1136/bmj.316.7134.823](https://doi.org/10.1136/bmj.316.7134.823)
45. Kahn, S. E., Hull, R. L., & Utzschneider, K. M. (2006). Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*, 444(7121), 840–846. DOI: [10.1038/nature05482](https://doi.org/10.1038/nature05482)
46. American Diabetes Association. (2013). Standards of medical care in diabetes—2013. *Diabetes Care*, 36(Suppl. 1), S11–S66. DOI: [10.2337/dc13-S011](https://doi.org/10.2337/dc13-S011)