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BASIC SCIENCE • LETTER TO THE EDITORS

Comments on "Increase in the circulating levels of malondialdehyde in patients with obstructive sleep apnea: a systematic review and meta-analysis"

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I read with interest a systematic review and meta-analysis of Fadaei et al. [1] entitled "Increase in the circulating levels of malondialdehyde in patients with obstructive sleep apnea: a systematic review and meta-analysis". The authors tried to pool available data to show the association between obstructive sleep apnea (OSA) and malondialdehyde (MDA) levels by meta-analysis of 14 published reports. MDA levels in the control groups varied in the range of 0.004 to 14.1 µmol/L (µM), and those of OSA groups were 0.0052 to 20.1 µM. Extreme heterogenecity was observed which could have originated from a number of possible sources: type of employed analytical method for determination of MDA (colorimetric, UV, spectroflourimetric and/or chromatographic methods), age of the sample donors in both control and OSA groups, their gender, and storage time of the samples. [2]. The large values of relative standard deviations in both control (varying between 17.4 to 312.8%) and OSA (varying between 0.5 to 62.2%) groups reveal that there are serious confounding factors affecting MDA levels in both groups. In addition, there are some points dealing with collecting MDA data reported in Table 2 of the review paper [1]; as examples, (1) MDA levels for control group (CG) and patient group (PG) were reported as 1.6 ± 0.4 and 2.6 ± 0.7 mM, whereas the reported data in the original paper (Ref #20 of [1]) were as 1.6 (1.5–1.8) and 2.6 (1.9–3.7) µM. Beside misquoted concentration unit of mM instead of µM, there is no straight and accurate procedure to calculate the standard deviations (as reported by Fadaei et al. [1]) from the range of MDA values. This is also the case for MDA data of Ref #26. A common way to estimate the standard deviation in these cases is dividing the range by 6, but this should be noted in the meta-analysis report. (2) The normal MDA values reported for the analytical method was 4.6–9.4 µM [3]; Asker et al. (Ref #28 of [1]) reported MDA levels for control group as 0.2 ± 0.1 Hmol/L! Interestingly, Hmol/L was a typographical error in the original paper of Asker et al., and it has been exactly repeated in Table 2 of the meta-analysis [1]. (3) Units of MDA were reported as nmol/L, mM or mmol/L, and µM and ng/mL. Using different concentration units poses difficulties in direct comparison of the data among various studies. We do not know if the values with different units were used in pooling the data or not? To facilitate the comparison, we convert all these data to µM and list in Table 1. (4) There were also typographical errors with MDA units of Refs. #20, #23, and #26. (5) There were more subgroups in the Yardim-Akaydin et al. study [18]; however, Fadaei et al. [1] discussed them in only three subgroups.

Fadaei et al. claimed that MDA is a robust marker of lipid peroxidation. It is obviously the most commonly used and one of the products of lipid peroxidation as well as a number of other biochemical reactions. It is a highly active compound and reacts with many biochemicals in serum/biological fluids. MDA is mainly determined after conversion to derivative compounds using a number of agents mainly thiobarbituric acid (TBA) which may also result in variations in its measured values using various analytical methods with different sensitivity and selectivity [2]. Oxidative stress may be observed in OSA due to dysfunction of the respiratory system. Different biomarkers have been presented for monitoring oxidative stress, and MDA is the most commonly used and a popular one in many clinical investigations. However, it has pitfalls concerning both application and analytical viewpoints. Some of these critiques on the reliability of MDA were simply ignored by the investigators [4, 5].

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Table 1 Details of the reported data for malondialdehyde (MDA) in control (CG) and obstructive sleep apnea (PG) groups

1st author	Status	Ref.[a]	CG/PG	MDA ± SD (μM)			Difference[b]
				CG	PG	Measurement method	
Ye	Mild	[24]	52/43	4.5 ± 1.2	4.6 ± 1.1	Kit 1	=
Ye	Moderate	[24]	52/39	4.5 ± 1.2	6.3 ± 2.1	Kit 1	<
Ye	Severe	[24]	52/45	4.5 ± 1.2	8.1 ± 2.9	Kit 1	<
Wang	Elderly	[16]	29/32	5.0 ± 0.7	6.2 ± 1.2	Kit 1	<
Wang	Non-elderly	[16]	23/51	4.1 ± 1.1	5.2 ± 1.5	Kit 1	<
Vatansever	Mild	[25]	24/9	0.9 ± 0.24[c]	1.0 ± 0.09[c]	HPLC	=
Vatansever	Severe[d]	[25]	24/17	0.9 ± 0.24[c]	1.2 ± 0.29[c]	HPLC	<
Jurado-Gámez		[20]	46/23	1.6 (1.5–1.8)[e]	2.6 (1.9–3.7)[e]	Kit 2	<
Chen	Mild	[22]	20/23	0.004 (0.0032–0.0042)[e]	0.0052 (0.004–0.0055)[e]	Flourimetry	
Chen	Moderate	[22]	20/21	0.004 (0.0032–0.0042)[e]	0.0059 (0.0049–0.0074)[e]	Flourimetry	
Wysocka	Pre-OSA-negative	[26]	22/22	5.86 (4.91–6.24)[e]	6.88 (6.08–8.53)[e]	UV	<
Wysocka	Pre-OSA-positive	[26]	22/22	5.89 (4.95–7.22)[e]	6.20 (5.36–7.35)[e]	UV	=
Yardim-akaydin	Mild	[18]	25/28	2.2 ± 0.91	3.0 ± 1.18	HPLC	<
Yardim-akaydin	Moderate	[18]	25/30	2.2 ± 0.91	3.0 ± 0.89	HPLC	<
Yardim-akaydin	Severe	[18]	25/59	2.2 ± 0.91	3.3 ± 1.1	HPLC	<
Ntalapascha		[19]	13/18	6.45 ± 1.02	6.82 ± 0.32	Colorimetric	=
Araujo		[27]	20/33	0.05 ± 0.01[f]	0.06 ± 0.02[f]	Kit 3	=
Lu		[21]	31/62	14.1 ± 4.1	14.8 ± 6.3	Kit 3	=
Asker		[28]	30/30	0.179 ± 0.56	0.698 ± 0.434[g]	UV	<
Li	Mild	[23]	33/41	4.6 ± 0.8[h]	5.4 ± 1.3[h]	Kit 1	<
Li	Moderate	[23]	33/40	4.6 ± 0.8[h]	6.7 ± 0.7[h]	Kit 1	<
Li	Severe	[23]	33/36	4.6 ± 0.8[h]	7.3 ± 1.1[h]	Kit 1	<
Cofta	Mild	[29]	26/26	2.7 ± 2.3[h]	7.8 ± 1.9[h]	Colorimetric	<
Cofta	Moderate	[29]	26/27	2.7 ± 2.3[h]	13.1 ± 1.7[h]	Colorimetric	<
Cofta	Severe	[29]	26/27	2.7 ± 2.3[h]	18.2 ± 3.2[h]	Colorimetric	<
Ekin	Mild	[30]	30/30	5.3 ± 1.1	7.6 ± 1.2	HPLC	<
Ekin	Moderate	[30]	30/30	5.3 ± 1.1	12.2 ± 3.1	HPLC	<
Ekin	Severe	[30]	30/30	5.3 ± 1.1	20.1 ± 5.6	HPLC	<

[a]Reference numbers in the review paper [1]

[b] = non-significant difference and < means CG < PG

[c]In the original work (Ref #25 of [1]), means standard errors were reported; we converted using $SD = SE \times \sqrt{n}$

[d]In the original work (Ref #25 of [1]), the subgroup called moderate-severe

[e]Range of variations were reported in the original works

[f]Values were converted to μM by dividing to 72.1 g/mol

[g]In the original work (Ref #28 of [1]), it was reported as 0.698–0.434

[h]In the original works, MDA values were shown graphically

Regarding the application viewpoint: "An ideal biomarker should possess a number of important characteristics including; 1) specificity for a pathological condition, 2) increase in response to a known stressor, 3) quantification method of the biomarker should be specific, precise, accurate and not interfere with other substances, 4) biomarker should be chemically stable, 5) be easily and cost-effectively measured at different time-points during clinical trials and monitored throughout the entire disease or treatment course, 6) be detectable in biological fluids of healthy individuals before the onset of a disease, 7) measurement should not be confounded by diet, 8) its value should not be influenced by other factors such as age, sex, stress, exercise or genetic determinants and 9) it should possess prediction capability to be used as an alternative to standard clinical assessment, disease progression or drug response and some other characteristics", [6] all of which are not fulfilled by MDA.

As detailed in a previous review article [2], the serious problems with MDA are:

- "Non-specificity of TBA reactivity on MDA

- Production of MDA from reactions other than lipid peroxidation
- Low efficiency of fatty acid hydroperoxids breakdown to MDA
- Effects of procedural modifications on MDA-TBA adduct development
- Low stability of MDA in biological samples due to the high tendency for reacting with proteins, amino acids etc. and rapid enzymatic degradation
- Poor reproducibility of analytical methods
- Low recovery data for the reported analytical methods." [2].

Concerning all these points, I would like to suggest the authors of systematic review and meta-analysis works to consider the validity of the published data before meta-analysis. As discussed in this communication, some reported MDA data are questionable and should be validated before pooling the data. The next point concerning the peer-review of these manuscripts is to spot-check some data from original works before writing the review report to the editor. I would like to recommend the clinical investigators validate (or at least partially validate) the analytical methods used to determine the levels of any biomarker of interest. Without validation of the method, the data are not reliable. A final point is not to use MDA as a biomarker of oxidative stress, since MDA may provide misleading findings [6].

References

1. Fadaei R, Safari-Faramani R, Hosseini H, Koushki M, Ahmadi R, Rostampour M, Khazaei H (2021) Increase in the circulating levels of malondialdehyde in patients with obstructive sleep apnea: a systematic review and meta-analysis. Sleep Breath in press https://doi.org/10.1007/s1132-021-02293-4
2. Khoubnasabjafari M, Ansarin K, Jouyban A (2016) Critical review of malondialdehyde analysis in biological samples. Curr Pharm Anal 12:4–17
3. Driessen C, Plomp RG, van der Spek PJ, Ince C, Kulik W, Mathijssen IM, Joosten KF (2013) Is there an effect of obstructive sleep apnea syndrome on oxidative stress and inflamatory parameters in patients with craniofacial anomalies? J Craniofac Surg 24:1908–1913
4. Wade CR, van Rij AM (1989) Plasma malondialdehyde, lipid peroxides, and the thiobarbituric acid reaction. Clin Chem 35:336
5. Hackett C, Linley-Adams M, Lloyd B, Walker V (1988) Plasma malondialdehyde: a poor measure of in vivo lipid peroxidation. Clin Chem 34:208
6. Khoubnasabjafari M, Soleymani J, Jouyban A (2018) Avoid using spectrophotometric determination of malondialdehyde as a biomarker of oxidative stress. Biomark Med 12:551–554