THE PATH AHEAD

Time to Change Standard of Care to Include Screening for Common Disease-Inducing Toxicants

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Abstract

Foundational to the standard of care is diagnosis of overt disease as well as testing for early predictors of future disease. Obvious examples of the later include measurement of blood pressure and cholesterol. The time has come to add to this thinking early detection of the environmental causes of disease. Substantial research now shows that metal and chemical contamination of the environment has resulted in body loads of these toxicants at high enough levels to induce disease. The time has come to add screening for toxicant load to the standard of care.

Introduction

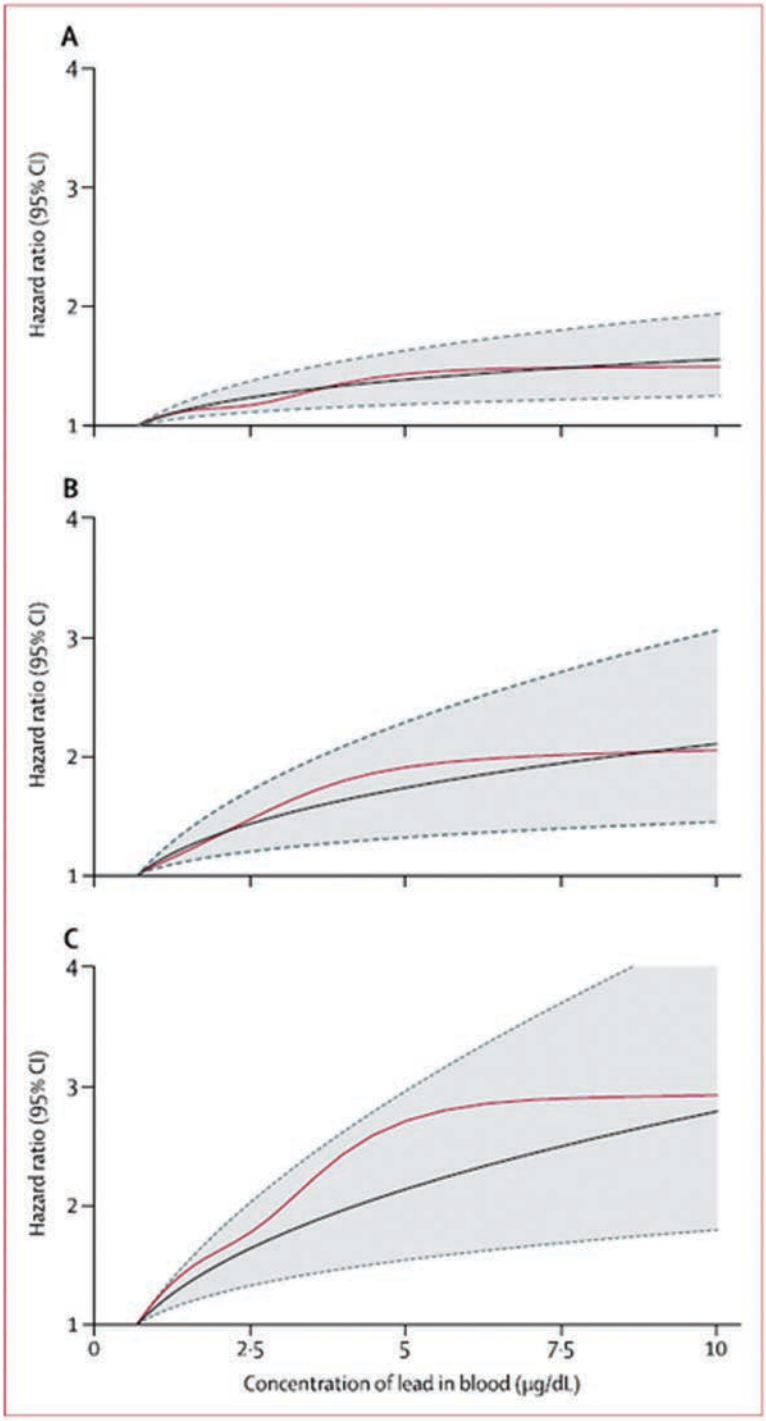
I have written many editorials on the substantial contribution of environmental toxins to disease burden (Is Mercury Toxicity an Epidemic? [8.1 & 8.2], Toxic Metal Elimination: We Need to Consider Oral, Not Just IV, Chelation [9.4], Persistent Organic Pollutants (POPs)—A Serious Clinical Concern [12.2], Is Mold Toxicity Really a Problem for Our Patients? Part I—Respiratory Conditions [15.2 & 15.3], Arsenic: The Underrecognized Common Disease-inducing Toxin [16.2], Particulate Matter is a Surprisingly Common Contributor to Disease [16.4], How to Practice Environmental Medicine [16.5], Toxin Exposure Reduction [16.6], Environmental Toxins and Infertility [17.2]). As I continue to dive into the research on the role of environmental toxins in inducing disease, the emerging picture is quite clear: environmental toxins have become the primary drivers of chronic disease. This leads to a clear mandate for all clinicians to help patients as soon as possible assess and reduce their toxic load and monitor as appropriate. (Note the use of the terms *toxicant* and *toxin*. Technically they are not interchangeable in the toxicology literature. Substances that cause adverse biological effects but are not produced by living organisms are defined as *toxicants*. As this journal is for clinicians, not research specialists, the commonly used term *toxin* is used to avoid unnecessary complexity.)

Lead

Lead plays a much bigger and more common role in disease than is currently recognized in the standard of care. A recent, substantial population-based study asserted that lead accounts for a stunning and worrisome 18.0% of all-cause mortality and 28.7 to 37.4% of cardiac mortality.[1] The following figure from this study is quite compelling. Note that the current "safe" level of blood lead is 10 ug/dL. As can be clearly seen, this level is very strongly associated with substantial disease risk.

The good news is that the public health elimination of most sources of lead has greatly decreased the level of lead in the general population. The bad news is that a significant portion of the population still suffers lead levels known to increase the risk of disease. The ugly is that a possible key reason for the dramatic increase in diagnosed disease around the age of andropause/menopause is the release of lead from bone as many in this age group are losing bone. The research looking at this possibility is limited, with the best being available on women. One study found that average lead levels in menopausal women is 39.0% higher (1.71 vs 1.23 ug/dL of blood) compared to menstruating women.[2] An earlier study found that if taking estrogen, the increase in menopausal blood lead does not happen.[3] The obvious assumption is that this was apparently due to the well-known bone protective effects of estrogen. Interestingly,

Figure 1. Lead concentration in blood



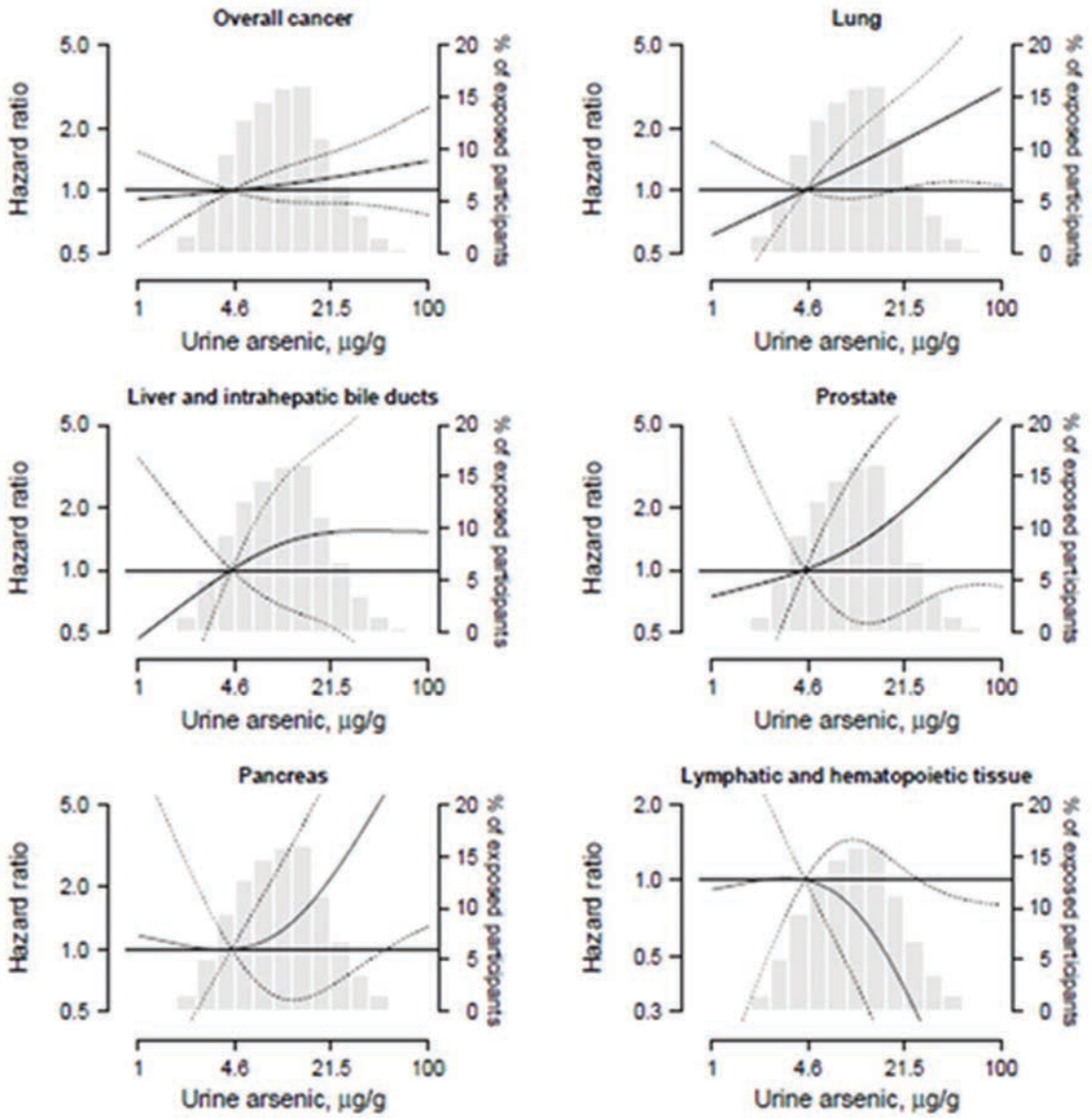
women in the top quartile of bone lead go into menopause 1.2 years earlier than those in the lowest quartile.[4]

Since lead is a powerful neurotoxin, childhood lead exposure appears to be predictive of adult neurodegenerative disease.[5] While the research cited in the article is mainly from cellular and animal research, there are enough human case reports to conclude this must be taken seriously.

Arsenic

Similar to lead, arsenic appears to cause a substantial portion of disease, especially several cancers. And, once again, the numbers are stunning. A comprehensive study of native Americans showed increased cancer risk within the supposedly safe levels of arsenic exposure—again, like lead. Comparing the top quintile to the lowest showed

Figure 2. Relationship Between Arsenic and Cancer[6]



statistically significant hazard ratios of 1.14 for all cancer mortality, and 1.34 for liver, 1.56 for lung, and remarkable 2.46 for pancreatic and 3.30 for prostate cancers.[6] Interestingly, arsenic appears protective from kidney cancer (HR 0.44) and lymphatic and hematopoietic cancers (HR 0.46). As can be seen in Figure 2, the relationship between arsenic levels and many cancers is dose-dependent. I must admit substantial curiosity why arsenic appears to impair hematological cancers.

Unfortunately, cancer is not the only disease strongly associated with arsenic. As discussed in editorial 16.2 *Arsenic: The Underrecognized Common Disease-inducing Toxin* co-authored with Walter Crinnion, ND, arsenic levels also show a dose-dependent correlation with peripheral neuropathy, cardiovascular disease, myocardial infarction, stroke, chronic obstructive pulmonary disease (COPD), gout, and diabetes.

I am currently diving into the research on genomics and toxin susceptibility. Too early to for a report (future editorial), but the first toxin I've looked into is arsenic and the genetic polymorphisms increasing its toxicity are surprisingly common, affecting about 20.0% of the population. Adding to this that 10% of the US public water supplies have arsenic levels known to induce disease (10 ug/L) in the average person. I think there is a lot here of substantial clinical significance.

Proposed Modification to Standard of Care

Ideally, every patient should be screened annually for toxin load. Toxicity is now so common it must be considered in every patient, especially in those with chronic disease, known exposure or losing bone. Obviously, it is too expensive to test for every metal and chemical toxin in the environment—my reading of the research

suggests at least 100 are in the environment at high enough levels to disrupt physiology and increase risk of disease. Nonetheless, I believe there is a cost-effective prioritization that should be considered. I suggest 2 strategies: screening for elevated toxic load and assessing the levels of specific toxins based on population probability of exposure or if an exposure is known.

There is very good reason to believe that decreasing toxin load can have a profound benefit. A very encouraging study evaluated the impact of decreasing lead levels (from banning lead in the 1970s) and decreasing cadmium levels (likely primarily from reduction in smoking as well as other public health measures) in the US from 1988 to 2004.[7] They determined the amount of death caused by these toxins due to damage to the cardiovascular system. They then calculated how many cardiovascular deaths were prevented by the reduction. While I am not sure all their adjustments were appropriate as several of them correlate with toxin load (eg, virtually every persistent organic pollutant and heavy metal increases with age, so adjusting for age under estimates the toxic effect), the numbers were quite compelling. They assert that 26.2% of the reduction in cardiovascular disease mortality is due to reduction of the body load of lead while 12.3% is due to reduction in cadmium. Yes, over a third. Please name me any other intervention that has yielded such a remarkable benefit.

GGTP (Gamma-Glutamyl Transpeptidase). GGTP (also abbreviated GGT) is a standard laboratory test used to help detect liver disease and bile duct obstruction. Of particular importance here, it increases within the "normal" range in proportion to toxic load. Not surprising since this enzyme recycles glutathione—a crucial body molecule involved in both detoxification and protecting against toxin-induced damage—and upregulated when more glutathione is needed. This inexpensive and readily available laboratory test is an effective screen for total body load for almost everyone. While it does not tell us which toxin(s) the patient is suffering, it helps determine which patients need additional screening. GGT has been shown to increase in proportion to many toxins, such as the heavy metals cadmium, lead, and mercury, commonly exposed chemicals like organochlorine pesticides and particulate matter high in polycyclic aromatic hydrocarbons—as well as alcohol and cigarette smoking.[8] Elevations—again within the "normal" range—show strong correlation with several diseases, including all-cause mortality.[9] The correlation with diabetes is the strongest (possibly an artifact of the toxin/diabetes connection having been studied the most so far). Those with a GGTP between 30-39—right in the middle of the "normal" range—have a 12-fold increased risk of diabetes.[10]

Two caveats when using this test as a screen: GGT clearly goes up in proportion to alcohol consumption so must be controlled for alcohol consumption. In addition, a small percent of the population does not have the genomics needed to upregulate GGTP in response to toxic exposure. These are likely our "yellow canaries," ie, the portion of the population even more damaged by toxic exposure than the general population.

At this time, I recommend screening for specific toxins everyone above 25 IU. A case can be made that this number could be as low as 10 IU, but there is simply not enough research yet to make such a recommendation. Another benefit of measuring GGTP is that it is an easy and inexpensive way to assess efficacy in decreasing toxic load.

Blood Lead. Everyone should have their blood lead periodically measured. Anyone with known exposure, losing bone or going through andropause/menopause should be measured annually.

The public health standard for "safe" levels of lead has decreased almost every decade the past half century. While the CDC's current threshold is 10 ug/dL of blood lead, this standard is likely to continue to decrease.

At this time, I recommend intervention above 2.0 ug/dL of blood lead. Most likely, no level of lead is safe.

Urinary and/or Toenail Arsenic. Arsenic is more complicated as genomics clearly impacts susceptibility to damage and ability to detoxify, and timing is important. Virtually all the research is based on urinary excretion levels. As the half-life of arsenic is only 2 to 4 days, urinary measurement must be done when the patient is in their normal environment and eating their most common diet. If that is not possible, toenail arsenic provides an estimate of historic exposure. However, the research on toenail arsenic is more limited.

My recommendation is that everyone's water supply should be tested for arsenic. If above 5 ug/L, the water supply needs to be cleaned up with appropriate filters. Everyone eating chicken and/or rice several times a week should be regularly tested. Everyone with cancer, except hematological, should be tested for arsenic. Those found to have significant arsenic exposure, should be regularly tested to ensure the arsenic reduction strategies are continuing to be effective.

I suggest a maximum urinary arsenic of 3.0 ug/g creatinine.

Conclusion

Is it possible that the old adages of "grumpy old men" and "female hysteria" are simply recognition of neurological dysfunction when these people are releasing neurotoxins from dissolving bone? Could it be that the huge increase in disease burden as people age into the 50s and 60s is simply a reflection of cumulative damage from toxic exposure, accumulation of difficult to detoxify, new-to-nature chemicals (the human half-life of PCBs is 3 to 25 years!) and the added burden from toxins released from dissolving bones?

Those interested in diving more deeply into environmental medicine will find Crinnion and Pizzorno, *Clinical Environmental Medicine, Elsevier* 2018 of value.

In This Issue

This is the third in our 3-issue series on the untold history of this medicine. We've worked to show the origins of the ideas underlying this medicine, key historic individuals, the professions that kept the ideas alive in the culture—despite huge medical opposition and personal cost—and the professions and associations continuing the advancement of this medicine.

The history series starts with an article I requested from therapeutic nutrition pioneers Alan R. Gaby, MD, and Jonathan V. Wright, MD. Although I was trained in nutritional medicine in my ND education, attending the monthly study club they hosted in the late 1970s dramatically increased my scientific understanding of the clinical application of nutrients. These remarkable clinician-teachers have advanced the practices of thousands of doctors and practitioners.

Integrative medicine leader and cofounder of AIHM (Academy of Integrative Health and Medicine) Mimi Guarneri, MD, tells us her story of moving from the world of conventional interventional cardiology to a fundamentally different understanding of health and disease. I have always been so impressed by her insistence that the new, rigorous integrative medicine association she helped create include *Health* in their name. I have often wondered if Health Medicine is a better name for what we are creating.

Associate Editor Jeffery Bland, PhD, finishes the history portion of this issue with an interesting presentation on the origins of functional medicine and the special people whose ideas and selfless work created a powerful paradigm for transformation of healthcare. He talks about the origins of many of the concepts in natural medicine (see The Natural Roots of Functional Medicine in IMCJ 17.1), key researchers whose pivotal work elucidated key mechanisms and highlights the Linus Pauling Functional Medicine Awardees who played a major role not just in advancing Functional Medicine, but also the key concepts underlying this way of thinking about truly curative medicine. I really like the characterization of functional medicine as an "operating system for integrating systems biology." It is profession-independent and honors the contributions regardless of origin. It is not a coincidence that many of these special people are closely associated with IMCJ. They serve as associate editors, review submissions as members of the editorial board, write articles and have been highlighted in interviews. We owe a huge debt of gratitude to these courageous and insightful medical pioneers, especially Jeff and Susan Bland for putting it all together to create functional medicine, David Jones, MD, who played an indispensable role in creating the clinical model that made functional medicine work for doctors and patients and Laurie Hofman, MPH, whose remarkable leadership and skills as CEO were crucial for development of the Institute for Functional Medicine into a highly successful and impactful organization.

Our conference interview by Managing Editor Craig Gustafson is of Lise Aschuler, ND, an expert in integrative oncology. Hard for me to adequately express how wonderful it is to learn from those who were once your students and see how they are bravely advancing the best medicine. An excellent read on true integrated care. Everyone with women patients suffering breast cancer should recommend her book where she describes her own journey and how the best of both worlds worked so very well. The history of her work facilitating collaboration is an interesting real-time look at the evolution of this medicine.

I love case series. They give a better sense of the complexity of assessing clinical impact when exploring a new intervention. I also like this approach, as compared to RCTs, as it allows more thoughtful consideration of the uniqueness of each patient and their health challenges. Katherine Hampilos, ND; Joshua Corn, ND; Wendy Hodsdon, ND; Peter Wagner, MD; Ryan Roop, MD; Elise Anderes, MD, and Lynn Troy, ND, describe their experiences with Carica papaya leaf extract on platelet count in a series of patients with chronic immune thrombocytopenic purpura.

Another of the several Case Reports in this issue is from Marika Alois, MD and Irene M. Estores, MD where they describe success using acupuncture and herbal medicines for a woman suffering PCOS. I think their thoughtful review of the literature an informative read.

The next Case Report is from Marika Alois, MD, and Irene M. Estores, MD, in collaboration with Brooke Scheller, MS, CNS; Cheryl Winter, MS, APRN, FNP-BC, BC-ADM, MS, RD, CDE, IFMCP; Jami Zamyad, MS, RD; Kerri Felmlee, MS, RDN, LD, CDE; Danielle Heard, MS, MS, CNS, LDN, INHC, doctoral students in clinical nutrition at Maryland University of Integrative Health Maryland. They describe their success using nutritional intervention for a patient with ulcerative colitis. I have used a similar protocol since the mid-1970s and can attest to its benefit for a wide range of gastrointestinal disorders. In fact, it has helped many patients with diverse diseases. An old naturopathic adage, states: "Disease begins in the gut."

The final case report is from Jené Andrea Carter, MS, MD(c); Sachi M. Desai, MS, DO(c); Jessica Probst, PT, DPT, MTC, and Mikhail Kogan, MD, describing their successful integrative medicine approach for a patient with peripheral neuropathy. I especially recommend reading the patient's perspective. She clearly articulated why patients come to us. I had seriously considered adding mercury to my screening suggestions above, but decided to limit to lead and arsenic as they are a bigger problem and the research showing benefit from their reduction is more robust. Nonetheless, as mentioned in my several editorials on mercury, I think mercury a huge public health problem.

After all these years of writing insightful and provocative BackTalks, seemed time to interview Associate Editor Bill Benda, MD. Craig provides us an interest

peeking at the pathway that brought Bill to integrative medicine. This is an important read for all of us. Remarkable insights into the history, challenges and future of integrative medicine. And thanks for the kind compliments Bill—means a lot to me. But most important, thank you for the incredible insight on how to solve resident burnout. Applies to everyone.

Which leads us to BackTalk. Thank you Bill for your inspiration and courage.

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References

1. Lanphear BP, Rauch S, Auinger P, et al. Low-level lead exposure and mortality in US adults: a population-based cohort study. *Lancet Public Health*. 2018 Apr;3(4):e177-e184. PMID: 29544878
2. Mendola P, Brett K, Dibari JN, Pollack AZ, et al. Menopause and lead body burden among US women aged 45-55, NHANES 1999-2010. *Environ Res*. 2013 Feb;121:110-3 PMID: 23352036
3. Korrick SA, Schwartz J, Tsaih SW, et al. Correlates of bone and blood lead levels among middle-aged and elderly women. *Am J Epidemiol*. 2002 Aug 15;156(4):335-43. PMID: 12181103
4. Eum KD, Weisskopf MG, Nie LH, et al. Cumulative lead exposure and age at menopause in the Nurses' Health Study cohort. *Environ Health Perspect*. 2014 Mar;122(3):229-34 PMID: 24398113
5. Reuben A. Childhood Lead Exposure and Adult Neurodegenerative Disease. *J Alzheimers Dis*. 2018;64(1):17-42 PMID:29865081
6. García-Esquinas E, Pollán M, Umans JG, et al. Arsenic exposure and cancer mortality in a US-based prospective cohort: the strong heart study. *Cancer Epidemiol Biomarkers Prev*. 2013 Nov;22(11):1944-53 PMID: 23800676
7. Adrian Ruiz-Hernandez, Ana Navas-Acien, Roberto Pastor-Barriuso, et al. Declining exposures to lead and cadmium contribute to explaining the reduction of cardiovascular mortality in the US population, 1988–2004 *International Journal of Epidemiology*, 2017, 1903–1912
8. Lee, D. H., & Jacobs, D. R. (2009). Is serum gamma-glutamyltransferase an exposure marker of xenobiotics? Empirical evidence with polycyclic aromatic hydrocarbon. *Clinical Chemistry and Laboratory Medicine*, *47*(7), 860–862. PubMed PMID: 19575547
9. Brenner, H., Rothenbacher, D., Arndt, V., et al. (1997). Distribution, determinants, and prognostic value of gamma-glutamyltransferase for all-cause mortality in a cohort of construction workers from southern Germany. *Preventive Medicine*, 26(3), 305–310. PMID: 9144754
10. Lee, D. H., Ha, M. H., Kim, J. H., et al. (2003). Gamma-glutamyltransferase and diabetes – a 4-year follow-up study. *Diabetologia*, 46(3), 359–364. PubMed PMID: 12687334