



EDELWEISS PUBLICATIONS
OPEN ACCESS

Review Article

ISSN: 2638-7735

Cardiometabolic Diseases: Biochemistry, Pathophysiology and Medical Innovations

Gundu HR Rao*

Affiliation: Laboratory Medicine and Pathology, Lillehei Heart Institute, Institute of Engineering Medicine, University of Minnesota, USA

***Corresponding author:** Gundu HR Rao, Emeritus Professor, Laboratory Medicine and Pathology, Lillehei Heart Institute, Institute of Engineering Medicine, University of Minnesota, Minneapolis, Minnesota, USA, Email: gundurao9@gmail.com

Citation: Rao HRG. Cardiometabolic diseases: biochemistry, pathophysiology and medical innovations (2020) Biochem Modern Appl 3: 1-5.

Received: Feb 10, 2020

Accepted: March 13, 2020

Published: March 20, 2020

Copyright: © 2020 Rao HRG. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

It gives us great pleasure, to write this invited overview on, Biochemistry, Pathophysiology and Medical Innovations, to the Journal of Biochemistry and Modern Applications. In an earlier article on a similar topic, we described about a biochemistry course, that is offered at the Cambridge University UK, called The Molecules in Medical Science, which focuses on diseases, that are familiar by name and of high relevance like diabetes and cancer. Harvard Medical School on the other hand, says, preparation of medical school in the 21st century, should reflect contemporary developments in medical knowledge, the pace of discovery and the permeation of biochemistry, cell biology, and genetics into most areas of medicine. Oxford Royale Academy looks at biomedicine the following way; -Biochemistry, as the name suggests, is where Biology meets Chemistry: it is the study of the living things, at a molecular level- or, to put it another way, the study of the very foundations of life. On the other hand, pathophysiology deals with a variety of altered metabolism, which drives the normal physiology out of gear, and promotes the development of risks, for various metabolic diseases. The Cardiometabolic Syndrome represents a constellation of metabolic abnormalities that are risk factors for the development of metabolic diseases, which in turn promote vascular diseases. Major metabolic diseases include hypertension, excess weight, obesity, and type-2 diabetes. Vascular diseases remain the number one killer worldwide, and have retained this status for over a century. There is considerable debate, about whether the treatment of the disease itself is superior, or just management of observed risks is enough? In view of such debates, there is a great need for the development of technologies that will facilitate early diagnosis and better management of progression, or regression of diseases. Furthermore, advances in research in the fields of genetics, cellular biology, molecular biology, and emerging diagnostic tools, will improve our ability to manage chronic cardiometabolic diseases. In this overview, we have discussed advances in the various fields, the disconnect that exists between the researchers and clinicians, as well as between technologists and the end-users.

Keywords: Hypertension, Chromatin remodeling, Gene expression, Oxidative stress, Monoclonal antibodies

Abbreviations: CVD-Cardiovascular Disease, CMD-Cardiometabolic Disease, PKC-Protein Kinase C, miRNAs-MicroRNAs, NIH-National Institutes of Health, T2D-Type-2 Diabetes, BPN- β -Type Peptide, PPG-Photoplethysmography, CTSAs-Clinical and Translational Science Awards, DM-Diabetes Mellitus, FPG-Fasting Glucose, OGTT-Tolerance Test, FDA-US Food and Drug Administration.

Introduction

Of the various metabolic diseases, obesity ranks number one, with more than 2.1 billion obese individuals globally (2013 figures, currently far greater number), then hypertension takes the second place, with over one billion hypertensive (1.1 billion in 2015) worldwide, and type-2 diabetes takes the third place, with close to half a billion diabetics. According to the European Society of Cardiology, depending on age groups, global diabetes prevalence is about 5% for the age group 45-59, 15% for the age group 55-59, and close to 20% starting at age group 65-69 years. Hypertension, also recognized as the 'silent killer' is among the most common diseases worldwide, and leading contributor to the acute vascular events, associated with heart attacks and stroke.

Hypertension is divided to two groups, primary (or essential) hypertension, which has no clear etiology and accounts for 85% of cases. The second group is called secondary, which accounts for less than 5% of cases [1-6]. A well-known risk factor for hypertension is the family history and increased sodium intake. Dietary salt is the most important factor contributing to hypertension. It is mainly attributed to impaired renal capacity to excrete sodium.

Other than therapeutic interventions aimed at improving sodium clearance from kidneys, major clinical trials have been aimed at modification of dietary sodium intake. In view of this fact, recommended dietary guidelines limit sodium to less than 2,300 mg per day. Smoking and excess consumption of alcohol, metabolic syndrome, and obesity are other risk factors. In addition, there seems to be a positive correlation between central abdominal obesity (South Asian Phenotype) and increased blood pressure. A landmark study, demonstrating the benefits of reducing salt intake on hypertension is the Inter Salt Study, which is a meta-analysis focusing on salt and blood pressure in 28 randomized trials.

At the cellular and molecular level, it has been shown that renal beta-2 adrenoreceptor stimulation in the kidneys leads, to decreased transcription of the gene encoding WNK4, a negative regulator of Na (+) reabsorption through Na (+) Cl (-) cotransporter in the distal convoluted tubes, resulting in salt-dependent hypertension [5,6]. How about the excess weight and obesity? The early origin of adult disease hypothesis suggests that obesity can develop in offspring from mothers exposed, to metabolic hardship or intrauterine growth



retardation. Studies are in progress to look at this phenomenon from cellular, molecular, and gene expression, as well as epigenetic influences. One of the proposed molecular mechanisms responsible for early-life metabolic programming is epigenetic modification of genes through methylation, histone modifications, chromatin remodeling, and noncoding RNA alterations. Excess weight and obesity; influence the development of type-2 diabetes the third triad of the metabolic syndrome. Hepatic insulin resistance, to a great extent contributes significantly, to the defective glucose homeostasis. Excess fatty acids, accumulation of triacylglycerol, and activation of novel Protein Kinase C (PKC) isoform PKC ϵ . Support for this hypothesis, comes from studies which demonstrated that PKC ϵ knockout mice exhibited, complete protection from high fat-diet induced glucose intolerance. It has been shown, that PKC ϵ directly phosphorylates the insulin receptor, which reduces insulin-stimulated tyrosine kinase and downstream signaling, resulting in hepatic insulin resistance [7-10].

MicroRNAs (miRNAs) are a class of evolutionary, conserved non-coding RNAs of 19-22 nucleotides that function as negative regulators of gene expression. In recent studies, there is cumulative evidence, demonstrating that Micro RNAs (miRNAs) are involved in the pathogenesis of Type-2 Diabetes (T2D), including in beta cells development, insulin sensitivity/resistance, insulin production/secretion, and insulin signaling. Platelet derived miRNA-103 has been found to negatively regulate the expression of secreted fizzled-related protein4, which is a potential biomarker for the onset of diabetes mellitus (pre-diabetes). MiRNA-103 seems to be down regulated in individuals with pre diabetes and expression of various mi RNAs, seems to be altered in patients with diabetes-related complications, including micro vascular complications. Several miRNAs have been identified as having physiological role in tissues, in which type-2 diabetes complications occur (liver, pancreas, adipose tissue and skeletal muscle). It is beyond the scope of this overview, to summarize the current knowledge of the impact of extracellular miRNAs, on the development of obesity-associated T2D, and its clinical complications, including endothelial and vascular dysfunction [11-15].

Now that we have briefly discussed the biochemistry and pathophysiology of major metabolic diseases such as hypertension, excess weight, obesity and diabetes, we will discuss some aspects of how to use these advances in biochemistry, cellular and molecular mechanisms, to develop precision and personal medicine. In view of the great advance made in the basic sciences, there is a great interest, investment, and call for action, regarding the use of precision and personal medicine. In a recent issue of JAMA (2019), Joyner and Paneth express their viewpoint on Cardiovascular Disease Prevention at Crossroads: Precision Medicine or Polypill. The authors state that: Just like polypill is a form of primary prevention, the precision medicine, is a form of secondary prevention, adding genomic information, to the array of tools available to health professional, to decide who, when, and how, to treat with the goal of preventing CVD.

President Barack Obama launched, a unique program during his State of the Union Address, on January 2015 "Tonight, I am launching a new Precision Medicine Initiative, to bring us closer to curing diseases, like cancer and diabetes- and to give all of us, access to the personalized information to keep ourselves and our families healthier." Francis Collins, the author of the article (Director of the Prestigious National Institutes of Health: NIH), explains that, "The initiative has a near-term focus on cancers, and a longer-term aim, to generate knowledge, applicable to the whole range of health and disease." This is a classic example of 'Top Down' approach, to find a solution, with no real hypothesis behind one of the largest publicly funded research project. At the time of this writing, Precision Medicine, as suggested by the experts is beyond the reach of majority of countries.

As regards personalized medicine, even in an advanced country like the USA, just a few cardiologists are incorporating personalized medicine, to clinical treatment [16-18].

Discussion

Metabolic risks factors include oxidative stress, inflammation, excess weight, hypertension, obesity, endothelial dysfunction, insulin resistance, hyperglycemia, diabetes, lipid abnormalities, sub-clinical atherosclerosis, and vascular diseases. As we have discussed above, there is a global approach, to find cure for chronic diseases like hypertension, obesity, and diabetes, incorporating recent advances in "Omics", along with the discoveries in the emerging science and technology areas. Alternate to the genomic approach suggested by Professor Francis Collins, researchers have suggested the management of disease itself, rather than the current focus on managing 'risk factors'. Professor Jay Cohn and associates, at the University of Minnesota, have developed a ten-point screening program, for early detection of Cardiovascular Disease (CVD) in asymptomatic individuals.

The tests include, recording; age, family history, personal history, smoking habits, arterial elasticity, blood pressure, optic fundus photos, micro albuminuria, ankle/brachial index, electrocardiogram, left ventricular ultrasound, and plasma type β -Type Peptide (BPN) levels. Each of the tests employed, can be categorized as normal, borderline, or abnormal. The seven vascular and 3 cardiac tests, according to these researchers, could yield an overall score of 0-20. The hypothesis being, that the disease score will be a sensitive guide, to the risk for a cardiovascular event [19]. From the clinician's perspective, when early disease is present, identification and aggressive treatment of modifiable risk factors, that contribute to disease progression becomes mandatory. Studies like INTEHEART and later studies from Harvard university researchers have proved beyond doubt, the benefits of managing modifiable risk factors for CVD, in reducing CVD-related premature mortality.

Studies from Harvard researcher's concluded; across four studies involving 55,685 participants, genetic and lifestyle factors, were independently associated with susceptibility to coronary artery disease. Among participants at high genetic risk, a favorable lifestyle was associated with a nearly 50% lower relative risk of coronary artery disease, than was unfavorable lifestyle. In a multicenter study, conducted in several industrial nations the researchers found, that cardiovascular disease mortality has declined, whereas, diabetes mortality has increased in these countries. All the metabolic diseases, including hypertension, obesity, and diabetes contribute significantly, to the development and progress of vascular diseases. Vascular diseases are the number one killers, and have remained at that status for over a century. Despite observed decline in CVD mortality in the industrial nations, contributing risks for the development and progress of CVD are rapidly raising worldwide [20-22].

Every major discovery in science and technology, has raised the expectation of the consumers, promised great opportunities, for revolutionary applications and therapy to the point, they have become the subject of Presidential announcements (President Barack Obama's State of the Union Speech of 2015). Basic science, starts with a hypothesis, and designs experiments that validate or reject it, with the goal of acquiring knowledge. Translational research starts, with a health need, and looks for scientific insights or tools to address that need. A translational scientist, should be able to move an idea all the way from basic, to a clinical application and back to the laboratory for more basic science. The need of the hour is establishment of translational science platforms. Why is it necessary? The science and technology are rapidly expanding and creating a gap in the knowledge-base, and its practical applications.



There is an immediate need for translation science, to bridge the disconnect between the clinicians and the researchers, technologist and the end users. In the United States, most training opportunities are through the Clinical and Translational Science Awards (CTSAs). Many academic Health Centre's have Clinical and Translational Institutes to help the clinicians and researcher's bridge the disconnect that exists. Since we are discussing Cardio metabolic diseases, Translational research centers have been established in major cities, for example, the SIBS-Novo Nordisk Translational Research Centre for Pre-Diabetes in Shanghai, China. During the past 30 years (1980-2010), seven national diabetes surveys were conducted in China mainland, indicating the prevalence of Diabetes Mellitus (DM) has increased by 17-fold.

According to researcher's, potential risk factors which could have contributed, to the increasing prevalence and incidence of DM and glucose intolerance in the Chinese population include; social and economic development, urbanization, dietary pattern, and Westernized lifestyle. This is the cost we pay for the progress in living. This is happening all over the world, and the progress that we see everywhere cannot be reversed. In an article in the recent issue of National Geographic, some experts say, modern humans should eat from a Stone Age menu. In the same article, the authors indicate that, it is the shift to processed foods, taking place all over the world that is contributing to rising epidemic of obesity and related diseases. We cannot stop the introduction of processed food worldwide. What are some alternate options, we have? We and others feel strongly, that primary prevention is the best choice we have.

When we consider primary prevention, what are the earliest interventions that we can develop? We have articulated earlier, about the low birth weight of children, and the origin of CMD in later life. In view of this fact, the primary intervention of CMD, should aim at reducing, or reversing, this intrauterine retardation of the fetal growth, which seems to predispose this cohort, to CMDs later in the adult life when discussing early diagnosis of the risk and robust intervention, childhood and adolescent obesity, is another important step that predisposes this cohort to CMDs. In addition, there is a huge population of pre diabetic worldwide. The statistics from China, India, and the USA with large population of diabetics, shows that in these countries, the pre diabetic population is larger than the diabetics [7,23,24].

Thirty-year intervention study, on Diabetes Prevention in China, showed that lifestyle interventions can delay the onset of diabetes, in people with impaired glucose tolerance, but whether this leads subsequently to fewer clinical complication or increased longevity is uncertain. In view of these encouraging results from China, it is worth concentrating on strategies, for intervention of this 'at risk' population from developing diabetes in later life. Early detectable markers are not well established, to detect pre-diabetes and as a result, it develops into diabetes. The diagnosis of both pre-diabetes, and diabetes, is based on glucose criteria; the common modalities used are Fasting Glucose (FPG) test, and oral Glucose Tolerance Test (OGTT). With the availability of continuous glucose monitors (Abbott and Dexcom), it is relatively is to monitor ambulatory interstitial glucose profiles (Figure 1).

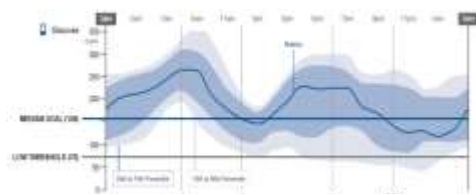


Figure 1: Ambulatory Interstitial Glucose Profile. (Courtesy: Abbott Diabetes Care).

Such emerging technologies, empower the patient not only to monitor glucose profiles, but also allows them to follow the effect of diet, physical activity, and lifestyle changes on the glucose levels. We have seen in recent years, development of number of non-invasive diagnostic tools, activity trackers, and health apps. We are validating some of these emerging technologies, in our effort to develop a comprehensive diagnostic platform for risk assessment, risk stratification, and risk prediction. Shown in the (Figure 2) are some of the LD-Technology (www.ldteck.com) products, used for assessment of cardiometabolic risks. This non-invasive diagnostic platform uses just three FDA (US Food and Drug Administration) approved devices, oximeter, blood pressure monitor, and galvanic skin response monitor [25].



Figure 2: Non-invasive diagnostic tools for assessing CMD risks (Courtesy: Dr Albert Maarek).

The manufacturers describe these systems as SudoPath system, TM Oxi system, and ES Complex system. Together, this platform performs several tests, to detect early stages of peripheral autonomic neuropathy, dysfunction of microcirculation, diabetic autonomic neuropathy, endothelial dysfunction, diabetes management, and detection of diabetes-related clinical complications (Figure 3). There is a great need for the development of noninvasive diagnostic platform, for the early detection of risks for the development of metabolic diseases. We are currently working on a project, in which we would like to use the advances made in the flexible piezoelectric pressure sensors.



Figure 3: Biomarkers for Cardiometabolic Diseases. (Courtesy: Dr Albert Maarek).

Basic idea is to use the flexible pressure sensors, to obtain pulse pressure wave forms, at various pulse points, and then to compute the velocity of the blood flow at regional vascular beds. In our recent articles, we have discussed non-invasive thermal imaging for monitoring vascular dysfunction in diabetic subjects [26,27]. David Rockefeller Professor Barry Collier's work focuses on molecular interactions between blood cells and blood vessels, and on new therapies for thrombotic disease, such as heart attack and stroke. Rockefeller University Newsletter describes, his innovation following way: By studying the receptors responsible for platelet aggregation and patients who genetically lack the receptors, Collier established the platelet α IIB β 3 (GPIIb/IIIa) receptor as an important target for antithrombotic therapy. This led him to develop monoclonal antibodies, to the platelet α IIB β 3 receptor, that inhibit platelet aggregation.



Working with scientists at Centocor, Collier helped develop a derivative of one of these antibodies into the drug abciximab, which was approved in 1994 to prevent ischemic complications of percutaneous coronary interventions, such as stent placement in patients with myocardial infarction and related conditions. More than five million patients worldwide have been treated with abciximab. A similar innovation in bench to clinic is the work of North Carolina State University researchers, which demonstrated the use of anti-IL-1 β platelet micro particles for cardiac detoxing and repair. In the introduction, we mentioned about a large study initiated in the USA, with the blessings of the then President, Barack Obama, and "Precision Medicine" [28].

Since the aim of this study, was to do genomics of more than one million Americans, with an assumption, that such a large study, will give us valuable information on the pathophysiology of the disease, and possible cure for cancer and diabetes, we described this attempt, as a study with no definite hypothesis. On the other hand as a part of this overall effort in 2017, Scripps Research, selected the first wearable, Fitbit for use in the ground breaking "All of Us program", based on the popularity and credibility of its use in peer-validated clinical research. "Collecting real-world, real-time data, through digital technologies will become a fundamental part of the "All of Us program," says Eric Dishman, director of the All of Us Research Program.

Thing to remember is the popular wearable that is used by over 60 million individuals, is the most commonly used tracker in biomedical research. More than 675 published studies have used Fit bit device. To get started, participants can log on to the All of Us participant portal at 'participant. Join Allof Us.org.' As a part of a retrospective longitudinal cohort study, Scripps Researchers from La Jolla, California, have published their findings of a preliminary study of 92,457 subjects. We have already mentioned in our studies on LD-Technology products, that integration of Photoplethysmography (PPG) sensors into a range of wearable's, has enabled the monitoring of heart rate measurements continuously over the life span. The future of such applications depend on the development health portals, and Apps, that can gather real-time data from multiple wearable devices or activity trackers, and compute risk assessment, risk stratification and risk prediction [17, 29-34].

Conclusion

Biochemistry, pathophysiology and Medical Innovations are complex topics, and are rapidly undergoing changes in view of the new findings and discoveries. As a result, the way modern healthcare is developed and delivered, is also undergoing constant revisions. Our work for more than four decades at the University of Minnesota Medical School, taught us the importance of multidisciplinary education and integrated approach to better modern healthcare, which is evidence-based. Dr. Francis Collins, the Director of NIH writes that potential to alter genes directly was first recognized nearly half century ago, yet application of this technology in modern medicine has not reaped its potential, in terms of therapeutic interventions. The story is the same, in stem cell research.

Professor Doris Taylor at the University of Minnesota, developed 'ghost hearts' from decellularized heart cell matrix, using stem cells derived from humans and claimed that bio artificial heart was weeks away. Translation of laboratory research to commercialization takes considerable time, and in view of this fact, there exists a disconnect between the innovators, researchers, teachers, and clinicians. This is true in device development, software analytics and algorithm applications as well. For instance, we have discussed the use of non-invasive diagnostic tool for early detection of cardiometabolic risks. The device, software and algorithms are very cleverly developed by Dr. Albert Maarek of LD-Technologies, Miami, Florida. Majority of the risk markers in these tests are software analytics and algorithm

based. Such modern applications, needs a robust independent validation regarding the specificity and accuracy of these calculated values. We have discussed briefly the importance of translational science platforms, to bridge the gaps between the students, clinicians, researchers, innovators, software developers and the health care providers. There is a great overall expectation, that the practice of medicine will change and introduce precision and personalized medicine in the near future. Similarly, there was considerable hope, that bio-artificial replacement parts will be available for repair of the dysfunctional body parts. Incorporation of the modern discoveries, innovations, and emerging technologies, will change the way healthcare is delivered, but it requires the education of a new generation of physicians, clinicians, translational scientists, researchers and technologists.

Beginning with the introduction in Harvard Medical School in 2006, of a curriculum called "New Integrated Curriculum" the Medical School has introduced revolutionary changes the way Medical Students are trained. The new curriculum emphasizes learning to learn, rather than routine memorization, and represents one of the most complete reforms of a US Medical School system. We sincerely hope that other medical institutions worldwide will incorporate such integrated approach to medical education. We also hope, that modern healthcare will also develop and incorporate an integrated approach to healthcare. As we have articulated in our earlier article, biomedical education is continuously evolving. For a long time, the basic sciences taught at the premier medical schools were, bacteriology, biochemistry, hematology and histology.

Modern day biomedicine in the broadest sense should provide needed insight into the underlying mechanisms of both structure and regulation that occur at the molecular, cellular, tissue, organ and whole system level. We have discussed the changes that are taking place at several medical institutions in their curricula. Like in any other specialized fields, the recent progress made in multiple disciplines is so rapid, it is hard to catch up, with all the emerging technologies, and integrate them in any curricula. Future of medicine, especially the precision and personal medicine, lies in clinicians gaining much more detailed information about the patient, the underlying causes of the disease, the knowledge of the emerging technologies, and their applications, to deliver personalized or precision treatment, with a better outcome. In a short overview like this, it is difficult to cover all aspects of modern biochemistry, pathophysiology of diseases, and mechanisms that underlie, we have just described a few relevant areas of this complex topic, readers are urged to refer to the relevant reviews, chapters and recent publications on these topics [35-39].

References

1. Bluher M. Obesity: global epidemiology and pathogenesis (2019) *Nature Rev Endocrinol* 5: 288-298. <https://doi.org/10.1038/s41574-019-0176-8>
2. Reilly JJ, El-Hamdouchi A, Diouf A, Monyekei A and Somda AS. Determining the worldwide prevalence of obesity (2018) *The Lancet* 391: 1773-1774. [https://doi.org/10.1016/s0140-6736\(18\)30794-3](https://doi.org/10.1016/s0140-6736(18)30794-3)
3. Bloch MJ. Worldwide prevalence of hypertension exceeds 1.3 billion (2016) *J Am Soc Hypertension* 10: 753-754. <https://doi.org/10.1016/j.jash.2016.08.006>
4. Mills KT, Bundy JD, Keely TN, Reed EJ, Kearney MP, et al. Global disparities of hypertension prevalence and control: A systematic analysis of population-based studies from 90 countries (2016) *Circ* 6: 441-450. <https://doi.org/10.1161/circulationaha.115.018912>
5. [Centers for Diseases Control and Prevention, USA.](https://doi.org/10.1161/circulationaha.115.018912)
6. Ando K and Fujita T. Pathophysiology of salt sensitivity hypertension (2012) *Ann Med* 44: S119-S126. <https://doi.org/10.3109/07853890.2012.671538>



7. Rao HRG. Fetal Origin of adult cardiometabolic diseases: Micronutrient and microRNA Interventions (2019) *EC Endocrinol Metab Res* 4: 7-16.
8. Barker DJ. Developmental origin of adult health disease (2004) *J Epidemiol. Comm Health* 58: 114-115.
9. Cordero P, Li J and Oben JA. Epigenetics of obesity: beyond the genome sequence (2015) *Curr Opin Clin Nutr Metab Care* 18: 361-366. <https://doi.org/10.1097/mco.0000000000000179>
10. Brandon AE, Liao BM, Diakanastasis B, Febbraio MA, Biden TJ, et al. Protein Kinase C epsilon deletion in adipose, but not in liver, improves glucose tolerance (2019) *Cell Metabol* 29: 83-191. <https://doi.org/10.1016/j.cmet.2018.09.013>
11. Yaribeygi H, Katsiki N, Benham B, Iranpanahe H and Sahebkar A. Micro RNAs and type 2 diabetes mellitus: Molecular mechanism and the effect of antidiabetic drug treatment. *Metabolism* (2018) 87: 48-55. <https://doi.org/10.1016/j.metabol.2018.07.001>
12. Vaishya S, Sarwade RD and Seshadri V. Micro RNA, proteins and metabolites as novel biomarkers for prediabetes, diabetes, and related complications (2018) *Front Endocrinol* 9: 180. <https://doi.org/10.3389/fendo.2018.00180>
13. Sebastani G, Manacarella F and Ventriglia G. Micro RNA mir124a, a negative regulator of insulin secretion, is hyper expressed in human pancreatic islets of type 2 diabetic patients. *RNA Dis* (2015) 2: 1-5.
14. Wang C, Wan S, Yang T, Niu D, Zhang A, et al. Increased serum microRNAs are closely associated with the presence of microvascular complications in type -2 diabetes mellitus (2016) *Sci Rep* 6: 20032. <https://doi.org/10.1038/srep20032>
15. Rome S. Are extracellular micro RNAs involved in type-2 diabetes and related pathologies? (2013) *Clin Biochem* 46: 937-945. <https://doi.org/10.1016/j.clinbiochem.2013.02.018>
16. Joyner MJ and Paneth N. Cardiovascular disease prevention at a crossroads: precision medicine or polypill? (2019) *J Amer Med Assoc* 322: 2281-2282. <https://doi.org/10.1001/jama.2019.19026>
17. Collins F and Varmus H. A new intuitive on precision medicine (2015) *New Engl J Med* 372: 793-795.
18. Lee M, Flammer JA, Lerman OA and Lerman A. Personalized Medicine in Cardiovascular Diseases (2012) *Korean Circ J* 42: 583-591. <https://dx.doi.org/10.4070%2Fkcj.2012.42.9.583>
19. Cohn JN, Hoke L and Whitman W. Screening for cardiovascular disease in asymptomatic individuals (2003) *Am Heart J* 146: 679-685.
20. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case control study *Lancet* (2004) 364: 937-952.
21. Khera AV, Emdin CA, Drake I, Natarajan P, Bick GA, et al. Genetic risk, adherence to a healthy lifestyle, and coronary artery disease (2016) *N Engl J Med* 375: 2349-2358. <https://doi.org/10.1056/NEJMoa1605086>
22. Di Cesare M, Bennet JE, Best N, Stevens AG, Danaei G, et al. The contribution of risk factor trends to cardiometabolic mortality decline in 26 industrialized countries (2013) *Int J Epi* 42: 838-848. <https://doi.org/10.1093/ije/dyt063>
23. Shen X, Vaidya A, Wu S and Gao X. The diabetes epidemic in China: an integrated review of national surveys (2016) *Endocr Pract* 22: 1119-1129.
24. [Gibbons A. The Evolution of Diet. National Geographic.](#)
25. Gong Q, Zhang P, Wang J, Ma J, An Y, et al. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30 year results of the + Da Qing Diabetes Prevention Outcome Study (2019) *Lancet Diab. Endocrinol* 17: 452-261. [https://doi.org/10.1016/S2213-8587\(19\)30093-2](https://doi.org/10.1016/S2213-8587(19)30093-2)
26. Choda G and Rao GHR. Diabetes related clinical complications: Novel approaches for diagnosis and management (2019) *J Clin Cardiol Diagn* 2: 1-8.
27. Choda G and Rao GHR. Thermal Imaging for the Diagnosis of Early Vascular Dysfunctions: A case Report (2019) *J Clin Cardiol Diagn* 2: 1-7. <https://doi.org/10.1126/sciadv.aay0589>
28. Zhenhua Li, Hu S, Huang K, Su T, Cores J, et al. Targeted anti-IL-1 β platelet microparticles for cardiac detoxing and repair (2020) *Sci Adv* 6: e0589. <https://doi.org/10.1126/sciadv.aay0589>
29. The "All of Us" Research Program: The All of US Research Program Investigators (2019) *N Engl J Med* 381: 668-676. <https://doi.org/10.1056/NEJMs1809937>
30. Quer G, Gouda P, Galarnyk M, Topol EJ and Steinhubl SR. Inter-and intraindividual variability in daily resting heart rate and its associations with age, sex, sleep, BMI, and time of year; Retrospective, longitudinal cohort study of 92,457 adults (2020) *Plos One* 15: e0227709.
31. Gandhi PG and Rao GHR. The spectral analysis of photoplethysmography to evaluate an independent cardiovascular risk factor (2014) *Int J Gen Med* 7: 39-47. <https://doi.org/10.2147/IJGM.S70892>
32. Gandhi PG, Rao GHR and Maarek A. Detection of neuropathy using sudomotor tests in type-2 diabetes (2015) *Degen Neurol Neuromusc Dis* 5: 1-7. <https://doi.org/10.2147/DNND.S75857>
33. Maarek A, Gandhi PG and Rao HRG. Identifying autonomic neuropathy and endothelial dysfunction in Type 11 diabetic patients (2015) *EC Neurology* 22: 63-78.
34. Rao HRG, Pratiksha G and Gandhi PG. Need for a non-invasive diagnostic platform for early detection and management of cardiometabolic disorders (2014) *J Clin Prevent Cardiol* 3: 93-98.
35. Rao HRG. Biomedical Education and Research: Expectations and Limitations (2018) *Biomed J Sci Tech Res* 9: 7076-7082. <https://doi.org/10.26717/BJSTR.2018.09.001787>
36. Martins IJ. Increased Risk for Obesity and Diabetes with Neurodegeneration in Developing Countries (2018) Avid science publishers, pp: 2-35.
37. Martins IJ. Anti-aging genes improve appetite regulation and reverse cell senescence and apoptosis in global populations (2016) *Advances in Aging Research* 5: 9-26.
38. Martins IJ. Single gene inactivation with implications to diabetes and multiple organ dysfunction syndrome (2017) *J Clin Epigenet* 3: 24. <https://doi.org/10.21767/2472-1158.100058>
39. Martins IJ. Sirtuin 1, a Diagnostic Protein Marker and its Relevance to Chronic Disease and Therapeutic Drug Interventions (2018) *EC Pharmacology and Toxicology* 6: 209-215.