



Family Risk of Metabolic Disorder; A Parameter for Timely Screening of Vascular Endothelial Health

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2017/31004

Editor(s):

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Complete Peer review History: <http://www.sciencedomain.org/review-history/18105>

Original Research Article

Received 14th December 2016
Accepted 23rd February 2017
Published 9th March 2017

ABSTRACT

Aim: To study the correlation of vascular endothelial health with family risk of metabolic disorders, in healthy overweight, obese and non obese subjects.

Study Design: A case-control (pilot) study.

Place and Duration of Study: The study was conducted in Cardiovascular Physiology lab, Department of Physiology, K.G.M.U from January 2009 to February 2010.

Methods: Cases and controls comprised of 30 overweight/obese healthy subjects (BMI \geq 25 kg/m² and/or WHR (female $>$ 0.85; male $>$ 1) and 30 non-obese healthy subjects respectively (BMI $<$ 25 kg/m² and/or WHR (female $<$ 0.85; male $<$ 1) excluding subjects with secondary cause of abnormal blood flow. Vascular endothelial health was assessed via reactive hyperemic response measured via impedance plethysmography in the subject's forearm. Fasting plasma glucose and serum lipid profile was also done.

Results: On comparison of biochemical variables, lipid derangement was recorded in both the groups. Significant difference in VLDL (control 21.84 \pm 9.68, case 29.01 \pm 16.83) (p=0.048) and TG

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(control 101.22±43.33; case145.21±84.02) ($p=0.013$), could be seen. VLDL & TG was deranged in 15 (6 cases + 9 controls) ($P=0.371$) and 14 (5 cases + 9 controls) ($P=0.222$) subjects respectively with no inter-group significant statistical difference. Inter-group reactive hyperemia at 1, 2, 3, 5, 7, 9 min post occlusion time showed no significant difference. Peak hyperemic response was seen at 2 minutes in both the groups. Though independent family history in first degree relatives of diabetes, coronary artery disease and/or hypertension showed a significant association with % RH at 2 min. ($P=0.049$), yet in group wise exploration, no significant association was seen.

Conclusion: Adverse anthropometry is universally not associated with deranged lipid profile and vice versa. Raised RH response associated with positive family risk could be either due to hyperinsulinemia and/or some yet undeciphered cause but not solely as add-on sequelae of deranged anthropometry (BMI & WHR).

Keywords: Reactive hyperemia; impedance plethysmography; vascular endothelial health.

1. INTRODUCTION

Background Metabolic disorders are a major contributor to the global non-communicable disease burden and family history is an important non-modifiable risk factor for the same [1]. According to our hypothesis, family risk of metabolic disorders (type 2 diabetes mellitus, hypertension, coronary artery disease) in healthy subjects does not result in a raised reactive hyperemic response.

Metabolic disorders are a major contributor to the global non-communicable disease burden. Family history is an important non-modifiable risk factor for the same [1]. The hereditary nature of metabolic disorders like hypertension, and diabetes is well established by numerous family studies [1-3] but still poor information is in literature about the role of family history of diabetes mellitus in the outcome of general population. Identification of early stages of atherosclerotic diseases is a fundamental step in the risk stratification protocols followed-up by physicians in order to have a complete overview about the clinical status of individuals with metabolic disorders This emphasizes the importance of early detection of vascular endothelial cell dysfunction (ECD) in subjects at risk of developing diabetes, a metabolic disorder. [4] Several factors contribute to ECD including smoking, high blood pressure, diabetes, high cholesterol levels, obesity, hyperglycemia, advance glycation end products (AGEs), and genetic factors [5,6]. Endothelial dysfunction is primarily due to reduction in nitric oxide (NO) bioavailability, a marker for vascular health which maintains vascular tone, inhibits platelet aggregation, vascular smooth muscle cell migration and proliferation and monocyte adhesion [7]. Endothelial dysfunction can result from and/or contribute to several disease

processes, as occurs in diabetes mellitus, hypercholesterolemia and hypertension [8]. Importantly, endothelial dysfunction has been shown to be of prognostic significance in predicting vascular events [9,10], so endothelial function testing may potentiate the detection of cardiovascular events likes myocardial infarction, peripheral vascular disease, ischemic stroke, and others [11,12].

It is an established fact that adiposity promotes intracellular inflammatory patho-physiological processes resulting in arterial damage leading to release of cytokines which harm cells by lowering cellular insulin sensitivity and presence of family risk accelerates and accentuates this process. But how absence of family risk modifies its course in ways different from ones with a family history needs further exploration. To date, variants in at least 65 genetic loci have been implicated in T2DM susceptibility which together explains approximately 10-11% of the variance [13]. Although genetic risk profiling for T2DM is offered by some companies, it does not currently have proven clinical utility [14,15]. Thus similar to T1DM, genetic counseling in cases of confirmed T2DM currently focuses on family history-based recurrence risk. The ADA recommends that early (before age 45) testing for T2DM (via fasting or random glucose, oral glucose tolerance test or HBA1c [glycosylated hemoglobin]) be considered in individuals who are overweight (body mass index [BMI] ≥ 25 kg/m²) and have one or more additional risk factors, one of which is a first degree relative with diabetes [16].

In the light of the above mentioned facts, this study aims to study endothelial cell function via assessing reactive hyperemia (RH) of peripheral conduit arteries, an indirect assay for nitric oxide, in response to oxygen debt and accumulation of waste products released by the vascular

endothelial cells due to temporary interruption (3-5 minutes) [17,18] of blood flow. Via an ambulatory non-invasive method of impedance Cardio-Vasography (ICVG) in apparently healthy subjects we intended to develop a mass screening protocol which could check vulnerable subjects from developing manifest metabolic disorders.

2. AIMS AND OBJECTIVE

2.1 Aims

To study the correlation of vascular endothelial health with family risk of metabolic disorders, in healthy overweight, obese and non obese subjects to develop a protocol for timely mass screening to check vulnerable subjects from developing manifest metabolic disorders.

2.2 Objective

- To analyze the role of anthropometric variables [body mass index (BMI), Waist-Hip Ratio (WHR)] on serum lipid profile and vascular endothelial health.
- To assess the impact of family risk of metabolic disorders on vascular endothelial health in healthy overweight, obese and non obese subjects in the light of their serum lipid profile.

3. MATERIALS AND METHODS

The study was conducted in Cardiovascular Physiology lab, Department of Physiology, K.G.M.U., Lucknow from January 2009 to February 2010, after an approval from one institutional Ethics committee, using STROBE guidelines.

Study design: A correlational, case-control study for confirmatory testing of the following hypothesis – Family risk of metabolic disorder (type 2 diabetes mellitus, hypertension, and/or coronary artery disease) in healthy subjects does not result in a raised reactive hyperemic response. Using one way approach, data was collected at one point for this fixed design, state problem.

Inclusion criteria - 30 overweight/obese healthy subjects with body mass index (BMI) $\geq 25 \text{ kg/m}^2$ and/or Waist hip Ratio (WHR) (female >0.85 ; male >1) and 30 non-obese healthy subjects (BMI $< 25 \text{ kg/m}^2$ and/or WHR (female <0.85 ;

male <1) [19-21] in the age group of 18- 45 years, of either genders.

Exclusion criteria - All subjects with any identifiable secondary cause of abnormal blood flow via history, clinical examination and fasting plasma glucose estimation. Identifiable secondary cause of abnormal blood flow included subjects with history of type 2 diabetes mellitus, hypertension, Coronary artery disease, toxin exposure, hypothyroidism, cervical rib, scleroderma, any state of systemic infection or inflammation, peripheral vascular disease, pregnancy, alcoholism, smoking, tobacco consumption, history of drug intake likely to alter endothelial function- oestrogen, ACE inhibitor, AT I receptor blockers (carvedilol) and fasting plasma glucose $\geq 110 \text{ mg/dl}$ [22].

A written informed consent was taken from all subjects screened under above inclusion and exclusion criteria and underwent the study. Keeping the fact in mind that endothelial function have a circadian pattern and vary seasonally and post prandially, the test was planned on overnight fasting subjects, during the morning hours.

The study involved the use of, Impedance Cardio-Vasography device Model- NICOMON (Larsen & Toubro) developed at the electronics division, Bhabha Atomic Research Centre, Mumbai (Jindal et al. 1985). It is an EPROM driven sine wave generator, which passes current of constant amplitude at 50 kHz frequency through body segment in patient mode with the help of isolation transformer and a relay. The same generator passes modulated sine wave current (1% amplitude modulation with triangular wave at 1 Hz frequency) through the calibration network of fixed resistance values in calibration mode. The voltage signal developed along current path is sensed via sensing electrodes and amplified using a differential amplifier. A high Q band pass filter outsources a rectified, filtered and buffered voltage signal Z i.e. the instantaneous electrical impedance of the body segment under investigation thus deriving $\Delta Z(t)$, dZ/dt and NdZ/dt signals. All the three are multiplexed via analog multiplexer. This multiplexed signal is filtered with the help of a second order, low pass filter having a cut off of 40 Hz for smoothening the waveform. Gain amplifier amplifies the wave using a multiplying DAC. Above wave is fed in dual analog to get Z signal during sync pulse and all the functions of Z during rest of heart period. A 12 bit analog to

digital convertor digitalizes the signals which are finally read through interface unit. The isolated ECG amplifier amplifies the ECG voltages by gain of 60 db which outsources to an adaptable threshold R wave detector and a multiplexer for giving the synchronization pulse to be used by PC for time sequencing the impedance data. Impedance Cardio-Vasography is a technique for detecting blood volume changes in a body part by changes in electrical resistance [23-25].

Before ICVG testing, the subject was made to lie supine comfortably on a couch with both the arms by the side in the level of his/her heart. Blood pressure cuff was tied in the left arm. Sensing electrodes V1 and V2, 25 cm apart, were applied around the forearm and the current electrodes I1 and I2 were applied at the neck and wrist respectively. In Electrocardiograph (ECG) recording procedure, three disc electrodes (lead I, II, III) are placed on the chest of the patient. One is placed in the area of the left shoulder, one in the area of the right shoulder, and one at the end of the sternum. Blood flow index (BFI) at rest was measured via ICVG followed by measurement of the blood pressure of the subject. Subsequently cuff pressure was raised to 200 mm Hg [26], for a period of 3 min. to occlude the arterial blood flow and was decided to produce adequate hyperemia (RH) but not to compromise patient's comfort. Subsequently pressure was released and brought down to 0 mm Hg. Following this, blood flow index (BFI) was again recorded at 1, 2, 3, 5, 7 and 9 minutes to see post occlusive reactive hyperemia (PORH) [23,24].

- BFI = maximum amplitude of NdZ/dt waveform (Normal range= 1.50 ± 0.31) [25]
- RH = [(Peak PO blood flow index – Resting blood flow index) / Resting blood flow index]
- % Reactive Hyperemia = [(Peak PO blood flow – Resting blood flow)/Resting blood flow] X 100

Inter-observer & Intra-observer variability coefficient for measurement of endothelial function via impedance plethysmography suggests that plethysmography is a suitable low-cost tool to assess baseline blood flow and post occlusive reactive hyperemia [27].

3 ml venous blood is later drawn for biochemical analysis of fasting plasma glucose and fasting lipid profile.

Statistical analysis was done using Statistical Package of Social Sciences, Version 15.0. Continuous data was represented as mean \pm SD. As parametric tests usually have more statistical power than nonparametric tests they are likely to detect a significant effect when one truly exists. Generally parametric tests assume that the data follow a normal distribution but surprisingly parametric tests can perform well with continuous data that follow nonnormal distribution, if sample size of each group be greater than 15 (2-sample t test). So we choose parametric test for comparing our nonnormally distributed data in two groups of overweight/obese vs. non-obese, independent sample t- test is used (Table 1). Non parametric tests like Mann-Whitney "U"/ Kruskal-Wallis have been used owing to dissimilarity in group sizes and their ability to handle outliers well. (Tables 3, 4, 5) Multivariate analysis is done for observation and analysis of more than one statistical outcome variable at a time. The confidence interval of the study was kept at 95%, hence a 'P' value less than 0.05 indicates a statistically significant difference.

3.1 Post-hoc Sample Size Calculation

$\alpha = .05$, $\beta = .2$, Power=70%

Sample size=60

4. RESULTS

A total of 60 subjects were enrolled in the study comprising of 30 cases and 30 controls. Male-female ratio was 1.5: 1 in both the groups. Mean age in control group and study group was 34 ± 13.11 and 40.77 ± 11.23 respectively. Case and controls were identified on the basis of anthropometric variables, BMI and WHR. The relative incidence of the anthropometric criteria for determination of obesity was 6.7% cases as WHR obese, 66.7% cases as BMI obese and 26.7% cases as WHR+ BMI obese.

On comparison of lipid profile of the two groups, serum VLDL (control 21.84 ± 9.68 ; case 29.01 ± 16.83) and serum TG (control 101.22 ± 43.33 ; case 145.21 ± 84.02) ($p = 0.013$), had statistically significant difference. ($p = 0.048$) Mean values of study group was found to be higher for all lipid profile parameters except HDL which was found to be lower as compared to control group (Table 1).

Table 1. Comparison of serum lipid profile in two groups

S. no	Parameter	Control group n=30		Study group n=30		Significance of difference P
		Mean	±SD	Mean	±SD	
1	Fasting plasma glucose (mg/dl)	99.59	8.67	100.13	9.88	0.821
2	Total cholesterol(mg/dl)	149.86	40.49	154.35	28.06	0.620
3	HDL(mg/dl)	42.44	9.32	39.25	10.24	0.212
4	LDL(mg/dl)	85.57	32.94	88.13	27.64	0.745
5	VLDL(mg/dl)	21.84	9.68	29.01	16.83	0.048*
6	Triglyceride(mg/dl)	101.22	43.33	145.21	84.02	0.013*
7	LDL/HDL Ratio	2.02	0.56	2.31	0.68	0.071

*Highly significant

On comparison of subjects with deranged lipid values in the control and study group, total cholesterol was deranged in 3 controls and 1 case (p=0.301); HDL was deranged in 15 controls and 17 cases (p= 0.605); LDL was deranged in 2 controls and 2 cases (p=1.000); VLDL was deranged in 6 controls and 9 cases (p=0.371); Triglyceride was deranged in 5 controls and 9 cases (p= 0.222); LDL/HDL was deranged in 2 cases and 0 controls (p=0.150). Thus maximum incidence of derangement was observed for HDL while minimum was observed for LDL/HDL ratio.

On comparison of control and study group for presence of cardiovascular risk factors (deranged lipid profile) 1 risk factor was recorded in 13 controls and 10 cases; ≥2 risk factors were recorded in 7 controls and 11 cases (p=0.514). Rest 10 controls and 9 cases had nil risk factors. Thus proportion of subjects with higher number of risk factors was higher in obese group.

The mean pre-occlusive BFI in the above 3 groups with varying number of cardiovascular risk factors (deranged lipid profile) showed that the mean value with no risk group was 1.87 ± 0.39 , with one risk factor was 1.63 ± 0.31 and with ≥ 2 risk factors was 1.54 ± 0.35 . Statistically a significant association between pre-occlusive blood flow and number of risk factors was observed (p=0.019). Thus, more the number of risk factors, lower is the baseline blood flow.

On comparison of mean pre-occlusive BFI between cases and controls, there were only 10 cases with raised BFI (7 controls + 3 cases). (p=0.166). Thus as compared to study group, the

proportion of subjects with raised pre-occlusive BFI was higher in control group.

On comparison of magnitude of % RH on a time scale in cases and controls, mean value at 1 min was 3.47 ± 16.46 and -0.17 ± 14.32 respectively (p=0.364); at 2 min. was 22.10 ± 21.77 and 21.10 ± 21.15 respectively (p=0.854); at 3 min. was 15.72 ± 16.97 and 19.06 ± 24.51 respectively (p=0.542); at 5 min. was 13.52 ± 16.99 and 14.84 ± 23.23 respectively (p=0.803); at 7 min. was 13.62 ± 17.07 and 15.99 ± 24.04 respectively (p=0.661); at 9 minutes was 8.98 ± 16.46 and 13.18 ± 26.04 respectively (p=0.458). Thus peak RH achieved was at 2 minutes in both the groups.

In group wise exploration, both control and study groups nearly bore the same relation to a family risk of metabolic disorder, cases (n=19/30) and controls (n=19/30) (Table 3). % peak RH (at 2 min) was seen to be higher in female subjects (0.34 ± 0.29), in subjects less than 30 years of age (0.33 ± 0.27), over-weight subjects on the basis of BMI (0.33 ± 0.31) and non-obese subjects on the basis of WHR (0.29 ± 0.24) (Table 4). On clubbing the two groups (overweight/obese and non-obese), the % peak RH (at 2 minute) was higher in subjects with positive family history of metabolic disorder (type 2 diabetes mellitus, hypertension, coronary artery disease) as compared to those without it. (p=0.049) (Table 5).

In multivariate analysis, peak reactive hyperemia (at 2 minutes) was observed to be having a significant association with Waist-Hip Ratio and resting blood flow index only (Table 2).

Table 2. Multivariate analysis

Model		Coefficients (a)						
		Unstandardized coefficients		Standardized coefficients	t	Sig.	95% confidence interval for B	
		B	Std. error	Beta			Lower Bound	Upper Bound
1	(Constant)	1.474	.547		2.693	.010	.373	2.575
	age	-.002	.003	-.120	-.706	.483	-.009	.004
	(F)glucose	.001	.003	.061	.446	.658	-.005	.007
	T.chl.	-.002	.003	-.245	-.626	.534	-.007	.004
	HDL	.004	.007	.155	.498	.621	-.011	.018
	LDL	.002	.004	.216	.377	.708	-.007	.011
	VLDL	.002	.007	.091	.222	.825	-.012	.015
	TG	.000	.001	.035	.088	.931	-.003	.003
	LDL/HDL	.024	.162	.065	.147	.884	-.303	.351
	BMI	.010	.008	.189	1.148	.257	-.007	.026
	W/H ratio	-1.271	.546	-.492	-2.328	.024	-2.369	-.173
	calories	9.29E-006	.000	.018	.108	.915	.000	.000
	resting blood flow index	-.298	.091	-.478	-3.282	.002	-.480	-.115

a Dependent Variable: Reactive Hyperemia

Table 3. Comparison of % RH at 2 min in two groups according to family risk of metabolic disorder

S. no	Family risk	Control group			Study group			Statistical significance
		Number of subjects			Number of subjects			
		(n=30)			(n=30)			
		n	mean	±SD	n	mean	±SD	P
1	negative	11	12.69	21.88	11	16.38	11.23	0.624
2	positive	19	28.02	20.78	19	23.84	25.08	0.585
P		0.069			0.361			

Table 4. Association of reactive hyperemia i.e. [(Peak PO blood flow – Resting blood flow)/Resting blood flow] with age, gender & anthropometric variables

(Proportions)		Mean	±SD	Significance of difference (P)*
S. no	Variable / Parameter			
Age				
1.	<30 Years (n=27)	0.33	0.27	0.204
2.	>30 years (n=33)	0.24	0.19	
Gender				
1.	Males (n=36)	0.25	0.18	0.174
2.	Females (n=24)	0.34	0.29	
BMI				
1.	Normal (<25 kg/m ²) (n=22)	0.25	0.12	0.927
2.	Overweight (25-30 kg/m ²) (n=27)	0.33	0.31	
2.	Obese (>30 kg/m ²) (n=11)	0.23	0.15	
WHR				
1.	Normal (<0.85 for females, <1 for males) (n=44)	0.29	0.24	0.341
2.	Obese (>0.85 for females, >1 for males) (n=16)	0.26	0.21	

Table 5. Relation of % reactive hyperemia at 2 min to family risk of metabolic disorder in clubbed group

S. no	Family risk	Mean	± SD	P
1.	Negative (n=22)	14.54	17.08	0.049*
2.	Positive (n=37)	25.88	22.87	

* Highly significant, n= number of subjects

5. DISCUSSION

The aim of the present study was to compare endothelial health in subjects with and without family risk of metabolic disorders. Because metabolic disorder lays its roots in the ground of obesity, initial subject selection was based on anthropometric measurements irrespective of family risk. Their lipid profile assessment reflected the non-universal association of deranged lipid profile with obesity and non-universal association of normal lipid profile with non-obese. The same rule applied to the presence of family risk of metabolic disorder also. We have literature that attributes development of insulin resistance and metabolic disorder in lean and thin subjects to the presence of family risk of metabolic disorders [28,29]. Such a pathophysiology in them was attributed to hyperinsulinemia and insulin-resistance of which hyperinsulinemia induces by itself an overall increase in the vascular impairment [26]. Martin et al. conducted a study to better understand the genetic influence on aggregation of metabolic syndrome phenotypes stating that as factors loading from the genomic and phenotypic correlational matrices are distinct, therefore reliance on phenotypic correlational alone may fail to disclose underlying genetic relationships [30].

It is known that the interaction between insulin and its endothelial cells' receptor is able to activate several biochemical pathways: 1) insulin receptor substrate-1 (IRS-1)/phosphatidylinositol 3-kinase (PI3K), related phosphorylation of Akt and activation of eNOS, thus progressive increase in nitric oxide (NO) production and consequent vasodilatation [31-33]; 2) activation of Ras/Raf/MAPK pathway whose ultimate action is the generation of endothelin-1 (ET-1), i.e. a molecule involved in the vasoconstriction, and its own receptor, ETA. Insulin resistance redirects the pathways activation towards ET-1 production:

in these conditions, the endothelium is not able to perform its normal function, the NO production is reduced and vasoconstriction prevails [31-33]. According to such a patho-physiology, nitric oxide activity seems to be affected much before any change in serum endothelin-1 levels is seen. If we follow that, a reactive hyperemic response caused by nitric oxide in such subjects with a positive family history should attenuate. But a converse result in our study indicates a yet undeciphered pathway which could explain an enhanced vasodilator response. Endothelium derived Hyperpolarizing factor (EDHF), a vasodilator is one such biochemical which gets up-regulated after a variety of pathologic conditions when nitric oxide mediated dilatations have been attenuation [34]. Thus it seems that bio-chemicals other than NO, but like EDHF or EDHF itself may be responsible for vasodilatation and hence hyperemia in subjects with a positive family history.

% peak RH (at 2 min) seen to be higher in female subjects in our study suggests the role of hormonal differences in causing differences in vascular reactivity and is consistent with the protective effect of estrogen on the vessel walls [35].

A progressive decline in endothelium – dependent vasodilatation with age as seen in our study is correlated with decreased endothelial vasomotor function [36].

The significantly decreased mean BFI, as the number of risk factors increased reflects additive effect of the deranged lipid variables over mean arterial blood flow.

Similar time of attaining peak RH in both the groups i.e. 2 minutes post occlusion time, suggested no endothelial malfunction. No doubt that obesity when compounded with metabolic disorders deranges endothelial function but as the abdominal obese group comprised of a smaller fraction in this study (33.4%), it can be stated that because of this, no statistically significant endothelial dysfunction was observed. It might be possible that 'quantitative criteria' in addition to 'morphological criteria' is required to determine the severity of obesity in a way that, more of subcutaneous obesity is required to trigger endothelial dysfunction in comparison to relatively less of visceral obesity, in triggering the same.

Our research contributions at the individual nodes of the hierarchy enlighten us, but also suggest many more questions and directions. Thus research on this domain can gradually be moved to a deeper level with a large sample size. Our study sample size though small but was just enough to provide the means to evaluate the technical aspects of the novel approach (endothelial health via plethysmography) while serving as a platform to generate preliminary data. Also the data collection which was exhaustive, encompassing demographic, clinical, and anthropometric, biochemical and biophysical data provide strength to our study.

6. CONCLUSION

In the light of our findings, we conclude that what seems as a favourable response i.e. a raised hyperemic response in subjects with a positive family history of risk factors, may be last ditch escape response before the vascular system succumbs to the inflammatory insult. Some yet undeciphered causes could thus be suspected of an adverse outcome and thus accordingly timely modified by lifestyle modifications or pharmacological interventions.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Priyanga Ranasinghe, Dilini N. Cooray, Ranil Jayawardena, Prasad Katuland. The influence of family history of Hypertension on disease prevalence and associated metabolic risk factors among Sri Lankan adults. *BMC Public Health*. 2015;15:576. DOI: 10.1186/s12889-015-1927-7
2. Barnett AH, Eff C, Leslie RD, Pyke DA. Diabetes in identical twins. *Diabetologia*. 1981;20:87–93. DOI: 10.1007/BF00262007) [PubMed]
3. Sebastien Bouret, Barry E. Levin, Susan E. Ozanne. Gene-environment interactions controlling energy and glucose homeostasis and the developmental origins of obesity. *Physiol Rev*. 2015; 95(1):47–82. DOI: 10.1152/physrev.00007.2014
4. Ciccone MM, Scicchitano P, Cameli M, Cecere A, Cortese F, et al. Endothelial function in pre-diabetes, diabetes and diabetic cardiomyopathy: A review. *J Diabetes Metab*. 2014;5:364. DOI: 10.4172/2155-6156.1000364
5. Goligorsky MS. Endothelial cell dysfunction: Can't live with it, how to live without it. *American Journal of Physiology*. 2005;288(5):F871–F880. [PubMed]
6. Deanfield J, Donald A, Ferri C, et al. Endothelial function and dysfunction. Part I: methodological issues for assessment in the different vascular beds: a statement by the working group on endothelin and endothelial factors of the European society of hypertension. *Journal of Hypertension*. 2005;23(1):7–17. [PubMed]
7. Patti G, Melfi R, Di Sciascio. The role of endothelial dysfunction in the pathogenesis and in clinical practice of atherosclerosis. *Recenti Prog Med*. 2005; 96(10):499-507.
8. Gopi Krishna Kolluru, Shyamal C. Bir, Christopher G. Kevil*endothelial dysfunction and diabetes: Effects on angiogenesis, vascular remodeling, and wound healing. *Int J Vasc Med*. 2012; 2012:918267. (Published online 2012 Feb 12) DOI:10.1155/2012/918267PMCID: PMC3348526
9. Corrado E, Rizzo M, Coppola G, Muratori I, Carella M, Novo S. Endothelial dysfunction and carotid lesions are strong predictors of clinical events in patients with early stages of atherosclerosis: A 24-month follow-up study. *Coronary Artery Disease*. 2008;19(3):139–144. [PubMed]
10. Perticone F, Ceravolo R, Pujia A, Ventura G, Iacopino S, Scozzafava A, et al. Prognostic significance of endothelial dysfunction in hypertensive patients. *Circulation*. 2001;104(2):191–6. [PubMed]
11. Bucala R, Tracey KJ, Cerami A. Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilatation in experimental diabetes. *The Journal of Clinical Investigation*. 1991;87(2):432–438. [PubMed]
12. Suuronen EJ, Hazra S, Zhang P, Vincent R, Kumarathasan P, Zhang Y, et al.

- Impairment of human cell-based vasculogenesis in rats by hypercholesterolemia-induced endothelial dysfunction and rescue with L-arginine supplementation. *Journal of Thoracic and Cardiovascular Surgery*. 2010;139(1):209–216.
[PubMed]
13. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segre AV, Steinthorsdottir et al. Diabetes genetics replication and meta-analysis (DIAGRAM) consortium. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet*. 2012;981–990.
[PubMed]
 14. Kuehn BM. Inconsistent results, inaccurate claims plague direct-to-consumer gene tests. *JAMA*. 2010;1313.
[PubMed]
 15. Mihaescu R, Meigs J, Sijbrands E, Janssens AC. Genetic risk profiling for prediction of type 2 diabetes. *PLoS Curr*. 2011;RRN1208.
[PubMed]
 16. American Diabetes Association. Standards of medical care in diabetes-2014. *Diabetes Care*. 2014;37(Suppl 1):S14-80. DOI: 10.2337/2014.
[PubMed]
 17. Bellin J, Joannidas R, Iacob M, Eltchaninoff H, Thuillez CH. Role of endothelium derived nitric oxide in sustained flow- dependent dilation of human peripheral conduit arteries. *Arch Mal Couer Vaiss*. 2003;96(7-8):738-41.
 18. Dakak N, Husain S, Mulcahy D, Quyyumi Arshed. Contribution of nitric oxide to reactive hyperemia: Impact of endothelial dysfunction. *Hypertension*. 1998;32(1):9-15.
 19. Executive summary of the clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults. *Arch Intern Med*. 1998;158:1855-1867.
 20. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: The evidence report. National Institutes of Health. *Obes Res*. 1998;6(Suppl 2):51S-209S.
[PubMed]
 21. DGSP: S 1- Leitlinie Vorsorgeuntersuchung im Sport; 2007.
 22. Alvin CP. Diabetes mellitus. In: Braunwald, Fauci, Kasper, Hauser, Longo, Jameson, editors. *Harrison's principles of internal medicine*. 15th ed. United States of America: The McGraw-Hill Companies, Inc. 2001;2109-2137.
 23. Bhuta AC, Babu JP, Jindal GD, Parulkar G B. Technical aspects of impedance plethysmography. *J Postgrad Med*. 1990; 36:64-70.
 24. Babu JP, Jindal GD, Bhuta AC, Parulkar GB. Impedance plethysmography: Basic principles. *J Postgrad Med*. 1990;36:57-63.
 25. Jindal GD. Impedance plethysmography for screening vascular disorders. *J Postgrad Med*. 1986;32:1-3.
 26. Arturo Sotomayor González, andrea kostine, Jorge Gomez-Flores, Manuel Cardenas. Non-invasive assessment of endothelial function. Intra and inter-observer variability. *Archivos de Cardiologia de Mexico*. 2006;76(4):397-400.
 27. Thijssen DH, Bleeker MW, Smits P, Hopman MT. Reproducibility of blood flow and post-occlusive reactive hyperaemia as measured by venous occlusion plethysmography. *Clin Sci (Lond)*. 2005; 108(2):151-7.
 28. Perseghin G, Ghosh S, Gerow K, Shulman GI. Metabolic defects in lean nondiabetic offspring of NIDDM parents: A cross-sectional study. *Diabetes*. 1997; 46(6):1001–1009.
[PubMed]
 29. Straczkowski M, Kowalska I, StepieÅ, A, Dzienis-Straczkowska S, Szlachowska M, et al. Insulin resistance in the first-degree relatives of persons with type 2 diabetes. *Med Sci Monit*. 2003;9:CR186-190.
 30. Martin LJ, North KE, Dyer T, Blangero J, Comuzzie AG, Williams J. Phenotypic, genetic and genome-wide structure in the metabolic syndrome. *BMC Genetics*. 2003;4(Suppl 1):S95.
[PubMed]
 31. Potenza MA, Addabbo F, Montagnani M. Vascular actions of insulin with implications for endothelial dysfunction. *Am J Physiol Endocrinol Metab*. 2009; 297(3):E568-77.
 32. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: Molecular and pathophysiological mechanisms. *Circulation*. 2006;113(15): 1888-1904.
 33. Ciccone MM, Scicchitano P, Cameli M, Cecere A, Cortese F, et al. Endothelial

- function in pre-diabetes, diabetes and diabetic cardiomyopathy: A review. *J Diabetes Metab.* 2014;5:364.
DOI: 10.4172/2155-6156.1000364
34. Robert M. Bryan, You J, Golding EM. Endothelium –derived hyperpolarizing factor: A cousin to nitric oxide and prostacyclin. *Anaesthesiology.* 2005; 102(6):1261-77.
35. Celemajer DS, Sorensen KE, Spiegelhalter DJ, Georgakopoulos D, Robinson J, Deanfield JE. Ageing is associated with endothelial dysfunction in healthy men years before age related decline in women. *J Am Coll Cardiol.* 1994; 24(2):471-6.
36. Bojia M, Djuria D, Petrovia J, Popovia Z, Tasia N, Petrovia B, et al. The effect of gender on vasomotor function of the vascular endothelium and cardiovascular remodeling during ageing. *Srp Arh Celok Lek.* 1999;127(3-4):101-8.

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