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ORIGINAL ARTICLE

Why early preventive check-ups matter: unmasking subclinical abnormalities in adults aged 18–45 via systemic ultrasound phenotyping (The LUMINA Score)

Yaroslav Bondarenko[1,2], Olena Pionova[1], Lidiya Cherkashyna[1], Kateryna Krasovska[1], Liliia Bobro[1], Olga Lakhno[1], Oksana Kauk[1]

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ABSTRACT

Aim: To evaluate systemic multi-organ ultrasound phenotyping using VScan Air™ CL for detecting subclinical abnormalities in healthy adults aged 18–45 years and develop an integrated scoring system (LUMINA System) for early risk stratification.

Materials and Methods: A prospective cohort study (2010–2025) enrolled 188 clinically healthy adults with normal biochemical markers, stratified into three age groups (18–26, 27–35, 36–45 years). Standardized ultrasound assessments of liver, kidneys, carotid arteries, heart, and thyroid were performed. The LUMINA System (score range: 0–29) integrated findings across organ systems.

Results: Subclinical abnormalities were detected in 79.8% of participants despite normal laboratory values. Early liver steatosis occurred in 20.7%, correlating with higher BMI, triglycerides, and HOMA-IR. Increased renal echogenicity was found in 28–35% despite preserved kidney function. Carotid intima-media thickness exceeded the 75th percentile in 22.6%, with progressive vascular stiffness. Thyroid abnormalities appeared in 47.35%, suggesting autoimmune activation. Mean LUMINA scores increased from 0.44±0.31 (18–26 years) to 12.12±3.68 (27–35 years), strongly correlating with BMI (r=0.68), waist circumference (r=0.71), and HOMA-IR (r=0.54).

Conclusions: Systemic ultrasound phenotyping enables early detection of multi-organ abnormalities in young adults with normal laboratory profiles. The LUMINA System provides unified preclinical risk stratification, revealing that metabolic, vascular, and endocrine remodeling coexist years before disease onset, enhancing preventive medicine through personalized intervention.

KEY WORDS: Vascular Remodeling, Ultrasonography, Risk Assessment, Young Adult, Preventive Medicine

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INTRODUCTION

Cardiovascular diseases, diabetes (DM), and chronic kidney and liver disorders remain leading causes of mortality despite major diagnostic and therapeutic advances [1]. Most individuals seek medical care only when pathology becomes clinically apparent, although its biological onset begins years earlier [2]. Among young adults, the prevalence of metabolic and behavioral risk factors is steadily increasing, yet conventional HCE-based risk models substantially underestimate their long-term vulnerability, creating a diagnostic gap and contributing to therapeutic inertia in the 18–45 age group [3]. The subclinical period—the "blind zone" of medicine—therefore represents a critical stage for transitioning from reactive treatment to proactive metaphylaxis.

Pathomorphological evidence shows that microcirculatory, parenchymal, and vascular alterations precede biochemical and clinical manifestations. Early hepatic steatosis predicts insulin resistance and T2DM [4]; subtle renal echogenicity changes indicate early nephropathy [5,6]; increased carotid intima–media thickness (CIMT) reflects endothelial dysfunction [7]; and reduced global longitudinal myocardial strain predicts future heart failure [8]. The thyroid gland is similarly sensitive to metabolic–immune imbalance, with diffuse hypoechogenicity, structural heterogeneity, or micro-nodules appearing before TSH or free T4 abnormalities [9]. Collectively, these alterations correlate with low-grade inflammation, cytokine dysregulation, impaired insulin sensitivity, altered lipid profiles, and endothelial reactivity, forming a unified multiorgan subclinical risk phenotype [10]. Detecting such changes in asymptomatic individuals provides a critical "window of opportunity" for early intervention.

This framework supports the hypothesis that multi-organ ultrasound phenotyping represents a universal

"ultrasound risk biomarker." The integration of conventional ultrasound with elastography, strain imaging, and vascular sonography enables preclinical stratification by aggregating minimal multiorgan deviations as sensitive indicators of systemic metabolic and endothelial stress. Within this paradigm, SUP (Sonographic Ultrasound Phenotyping) is proposed as a multimodal quantitative approach capable of detecting early multiorgan structural and functional alterations. To translate these findings into an integrative vulnerability metric, the LUMINA framework (Long-term Ultrasound-Metabolic Integrated Assessment) shifts risk assessment from traditional HCE models toward estimating Biological Age or a consolidated Phenotypic Risk Score (PRS) based on previous publications [11-16]. The scientific novelty lies in the transition from organ-centric diagnostics to preclinical multisystem phenotyping and metaphylaxis, enabling risk modification before symptom onset. An individualized "ultrasound passport" for young adults, with regular monitoring of key quantitative parameters, may enhance primary care by enabling early risk identification and timely personalized prevention, ultimately reducing the long-term burden of chronic diseases.

AIM

To evaluate systemic multi-organ ultrasound phenotyping using VScan Air™ CL for detecting subclinical abnormalities in healthy adults aged 18–45 years and develop an integrated scoring system (LUMINA System) for early risk stratification.

MATERIALS AND METHODS

This prospective longitudinal cohort study (2010–2025) progressed over the years through sequential stages refining systemic ultrasound phenotyping and integrating accumulated data into the final protocol. The analysis included 188 clinically healthy adults aged 18–45 meeting strict inclusion criteria, the population study was conducted on Caucasians. Laboratory parameters (glucose, creatinine, ALT, AST, lipid profile) were within reference ranges; manifest chronic somatic disease led to exclusion. In a small subgroup, additional biomarkers—ApoB, TNF-α, IL-6—were measured using high-sensitivity ELISA (see Supplementary Materials). The population was stratified by age: 1-st group — 18–26 years (n = 68; 36.2%), 2-nd group — 27–35 years (n = 70; 37.2%), 3-rd group — 36–45 years (n = 50; 26.6%), enabling analysis of age-related subclinical dynamics within a homogeneous young adult cohort and ensuring adequate statistical power to detect age-dependent changes. All participants signed informed consent (Declaration of Helsinki and GDPR, Art. 6 Abs. 1 lit. a). The study was approved by the Ethics Committee of Kharkiv National Medical University (approval No. 4, date: 01.04.2026).

All participants underwent standardized anthropometric assessment (BMI, waist circumference), blood pressure measurement, and comprehensive ultrasound using the portable expert-class VScan Air™ CL system (GE Healthcare). All scans were performed by a single researcher to minimize variability, digitally stored, and independently reviewed by two blinded experts. The ultrasound protocol covered five organ systems. Liver echogenicity, structure, and steatosis were assessed, with elastography when feasible. Kidney evaluation included size, parenchymal thickness, cortico-medullary differentiation, echogenicity, and resistive index as a marker of microvascular dysfunction. Carotid arteries and jugular veins were examined for intima–media thickness and focal remodeling. Standard echocardiography assessed diastolic function (E/A and E/e' ratios) and included strain analysis. The thyroid gland was evaluated for volume, echostructure, vascularity, and asymptomatic nodules according to TIRADS criteria [17].

Data processing was performed centrally. Quantitative variables were described as mean values and standard deviations (mean ± SD), Median (IQR) and qualitative variables as percentage frequencies. Comparisons between groups were carried out using the Student's t-test for independent samples or the χ^2 test. Correlation analysis was performed using Pearson's or Spearman's method (ρ). The statistical significance was set at $p < 0,05$.

SUPPLEMENTARY MATERIALS

https://docs.google.com/document/d/1tiy1UhuS1--I-5xmcYsJ2S-S94RkXvHKXsj6MYooHbQ/edit?usp=sharing

AI STATEMENT

The author states that no AI tools were used in writing this article.

RESULTS

THE LIVER AS AN EARLY ULTRASOUND MARKER OF METABOLIC RISK

The liver is a key organ of metabolic regulation that responds sensitively to changes in lipid and carbohydrate metabolism, and increased echogenicity of

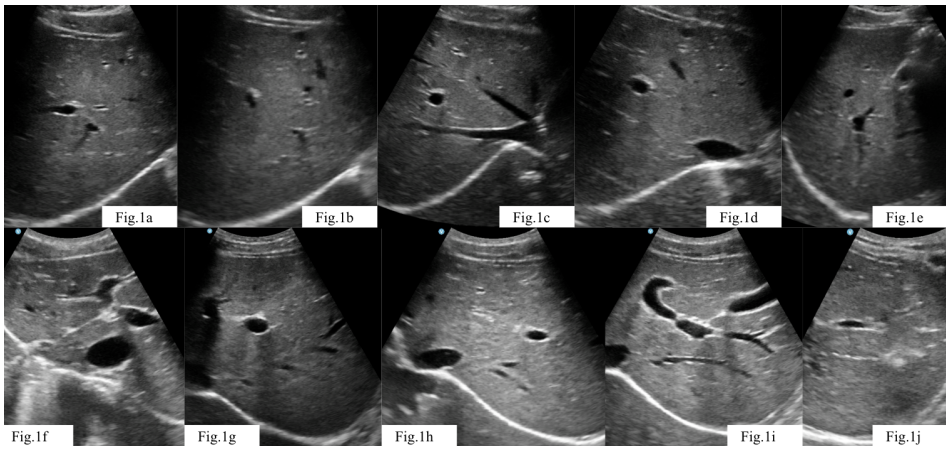


Fig. 1. Ultrasound features of the liver in the 18–26 age group
Picture taken by the authors

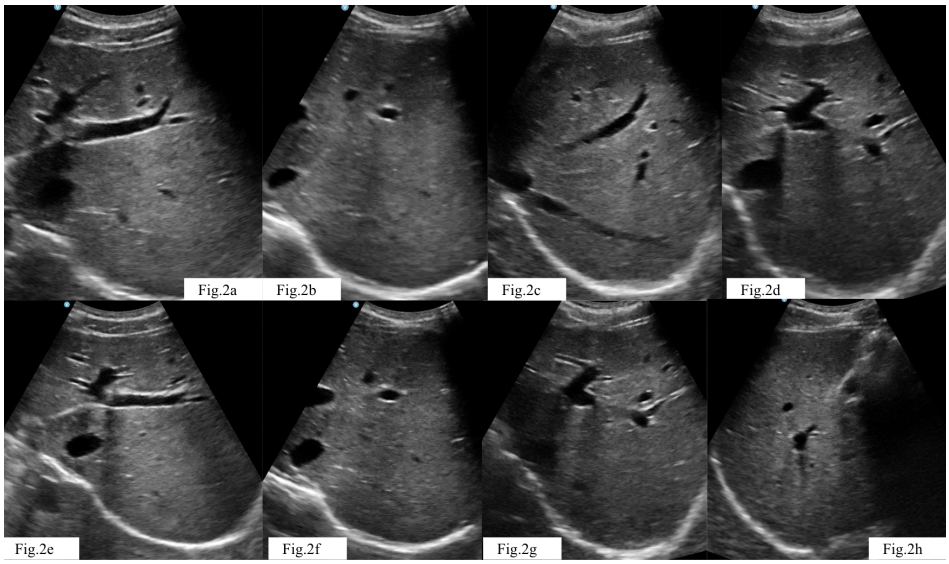


Fig. 2. Ultrasonic features of the liver in the 27–35 age group
Picture taken by the authors

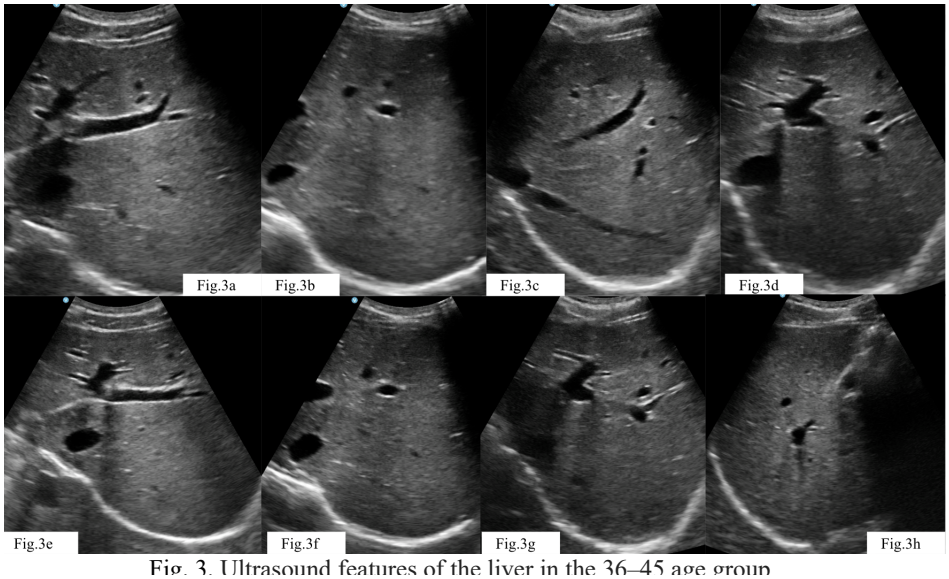


Fig. 3. Ultrasound features of the liver in the 36–45 age group

Fig. 3. Ultrasound features of the liver in the 36–45 age group
Picture taken by the authors

its parenchyma serves as one of the earliest markers of metabolic disturbances [18]. This phenomenon reflects the accumulation of TG in hepatocytes, which alters the acoustic properties of the tissue, and can be detected by ultrasound even before laboratory abnormalities appear [19]. In a cohort of 188 participants, increased parenchymal echogenicity, consistent with early hepatic steatosis, was detected in 39 individuals (20.7%). In addition, increased liver echogenicity was connected with early insulin resistance despite normal fasting glucose and HbA1c levels [20]. Subclinical steatosis was accompanied by higher fasting insulin

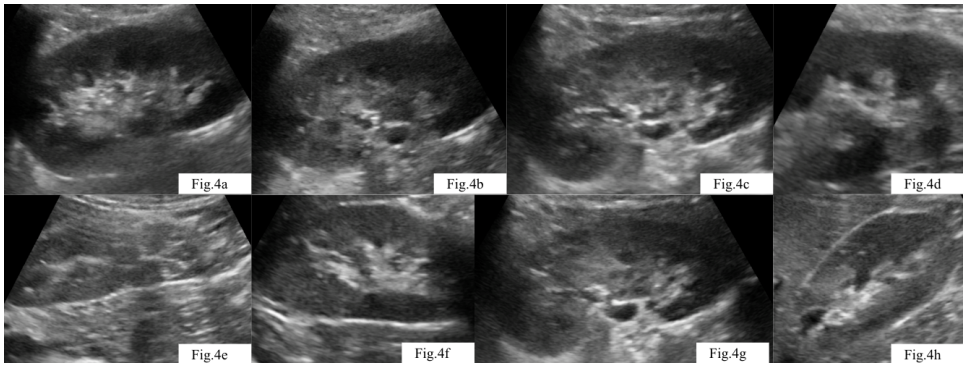


Fig. 4. Morphometric and microvascular characteristics of kidneys in young adults (18–26 yrs)
Picture taken by the authors

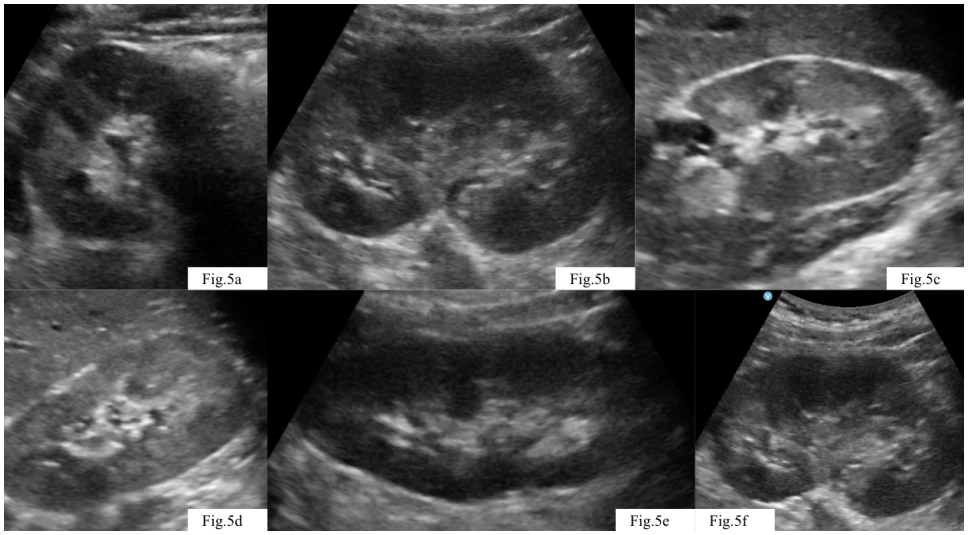


Fig. 5. Morphometric and microvascular characteristics of kidneys in middle-aged adults (27–35 yrs)
Picture taken by the authors

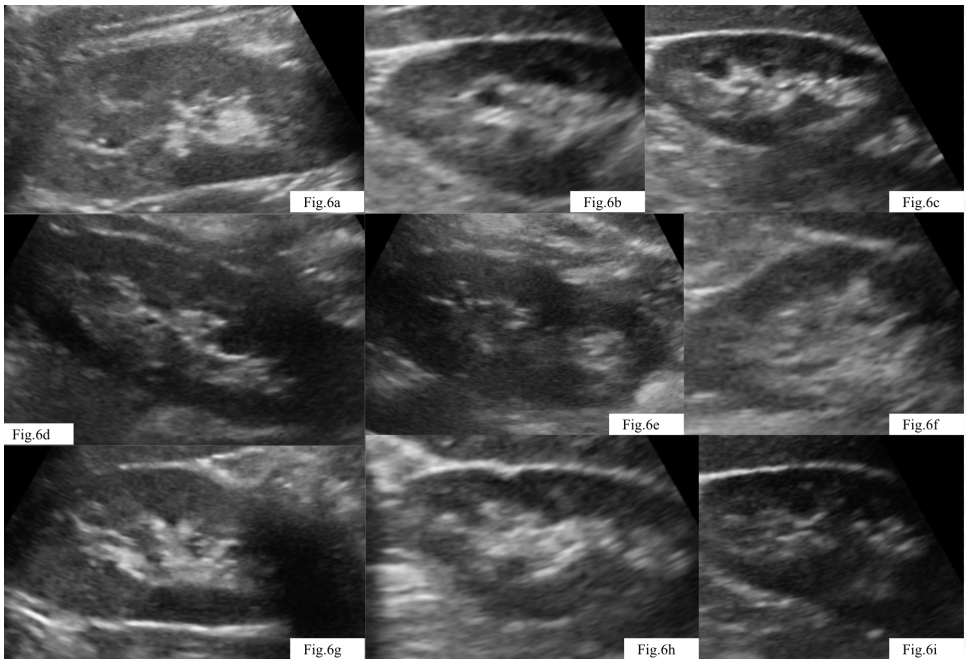


Fig. 6. Morphometric and microvascular characteristics of kidneys in older adults (36–45 yrs)
Picture taken by the authors

(4.44–20.28 μIU/mL), elevated HOMA-IR (1.09–4.74), and increases in TG (1.84±0.40 mmol/L), LDL-C (3.66±0.57 mmol/L), and pro-inflammatory cytokines (TNF-α 3.75±0.60 pg/mL; IL-6 12.56±0.88 pg/mL), indicating low-grade inflammation that promotes insulin resistance [4, 21, 26].

T**he 2-nd group** demonstrated a statistically significant increase in BMI and waist circumference compared with the 1-st group ($p<0.05$), that indicates early development of the abdominal component of metabolic syndrome. In this group, moderate hepatic echogenicity corresponded to early subclinical steatosis and was consistent with ele-

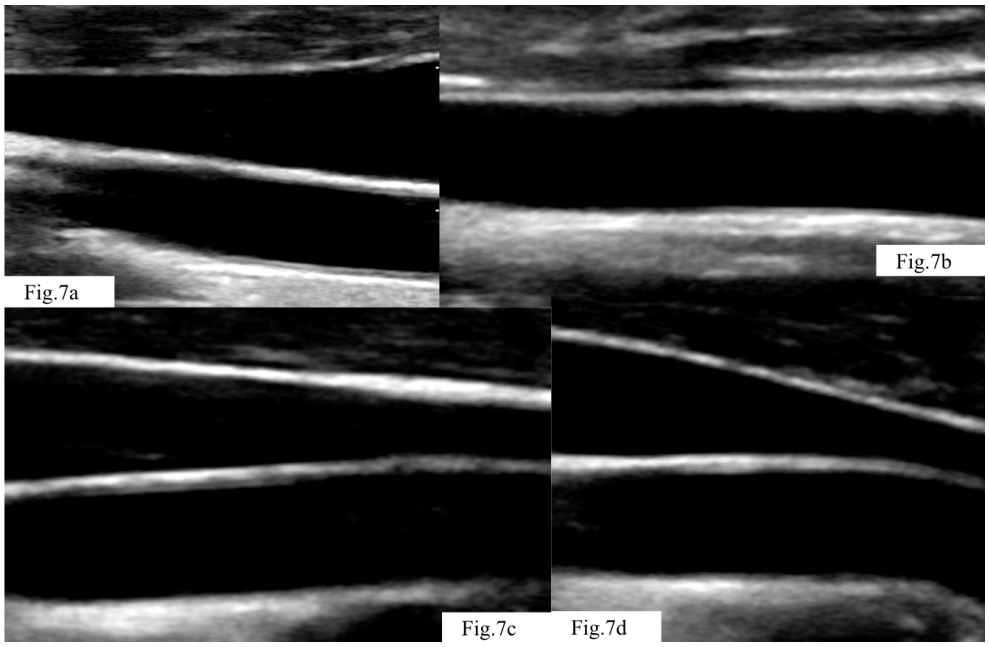


Fig. 7. Morphometric and hemodynamic characteristics of the common carotid arteries in the 18–26-year age group (control phenotype)
Picture taken by the authors

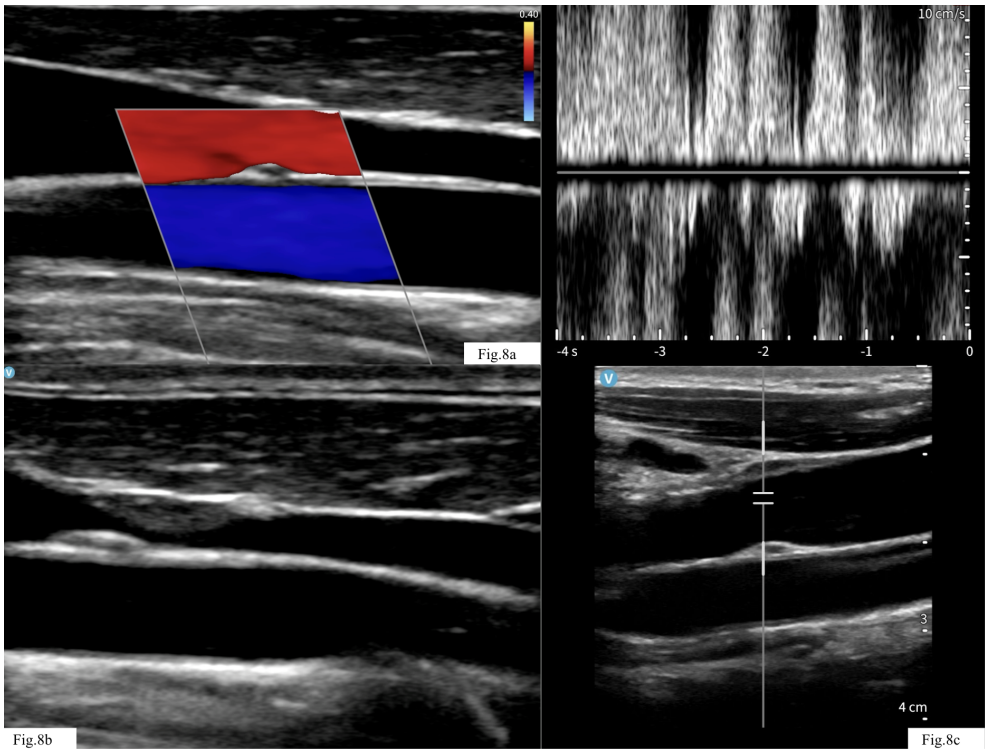


Fig. 8. Ultrasound documentation of early atherogenic mass formation with minimal stenotic changes (<25%)
Picture taken by the authors

vated BMI and waist circumference. Despite the increased anthropometric indices, glycemia, liver enzymes, and lipid profile remained normal, suggesting preserved metabolic compensation [28]. Ultrasound findings confirmed increased echogenicity characteristic of early steatosis with maintained liver function, as described by Mathiesen et al. (2002) [22]. This stage likely reflects a "window of metabolic vulnerability," during which structural liver alterations precede detectable biochemical disturbances. In the 1-st group, no structural liver abnormalities were identified. Echostructure remained homogeneous with a preserved vascular pattern, confirming intact hepatocellular homeostasis. These findings reflect the high adaptive capacity of the young liver, supported by efficient antioxidant defense and fatty-acid oxidation systems, serving as a physiological benchmark of early metabolic stability. In the 3-rd group, increased liver echogenicity was observed in only ~6% of participants and corresponded to minimal steatosis with preserved hepatic function. These individuals had borderline-normal anthropometric parameters without abdominal obesity. The low prevalence of steatosis in this group suggests a shift in systemic metabolic regulation: enhanced β-oxidation and activity of the AMPK–SIRT1–PPAR-α axis limit hepatic lipid accumulation, while the

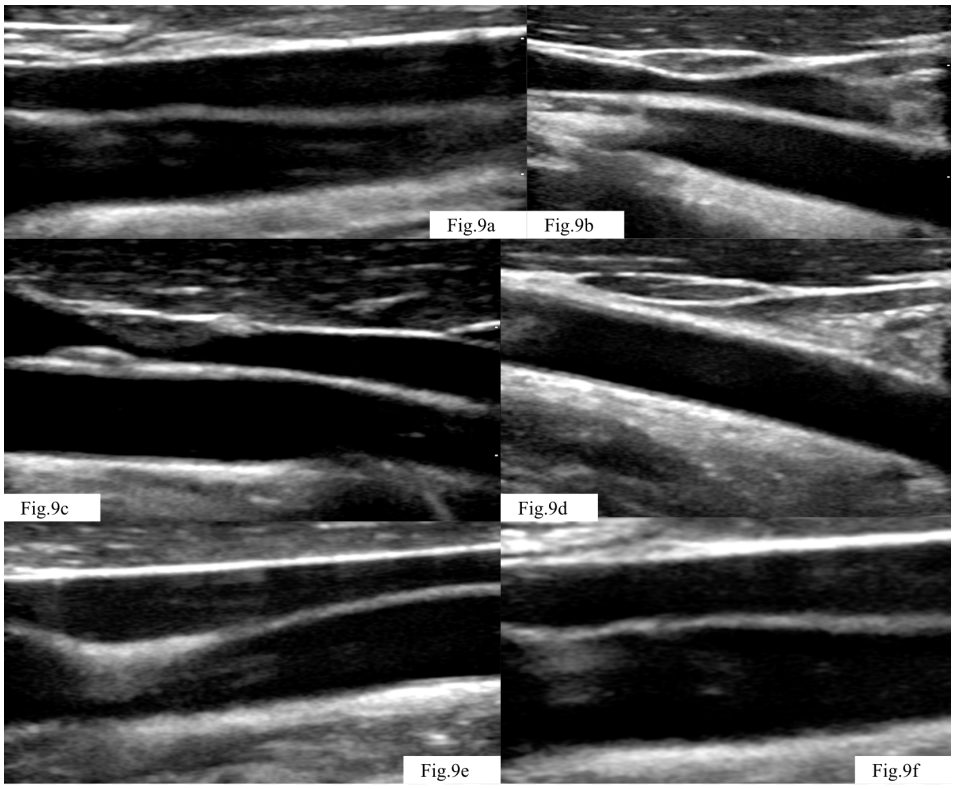


Fig. 9. Early morphologic alterations in the 27–35-year age group
Picture taken by the authors

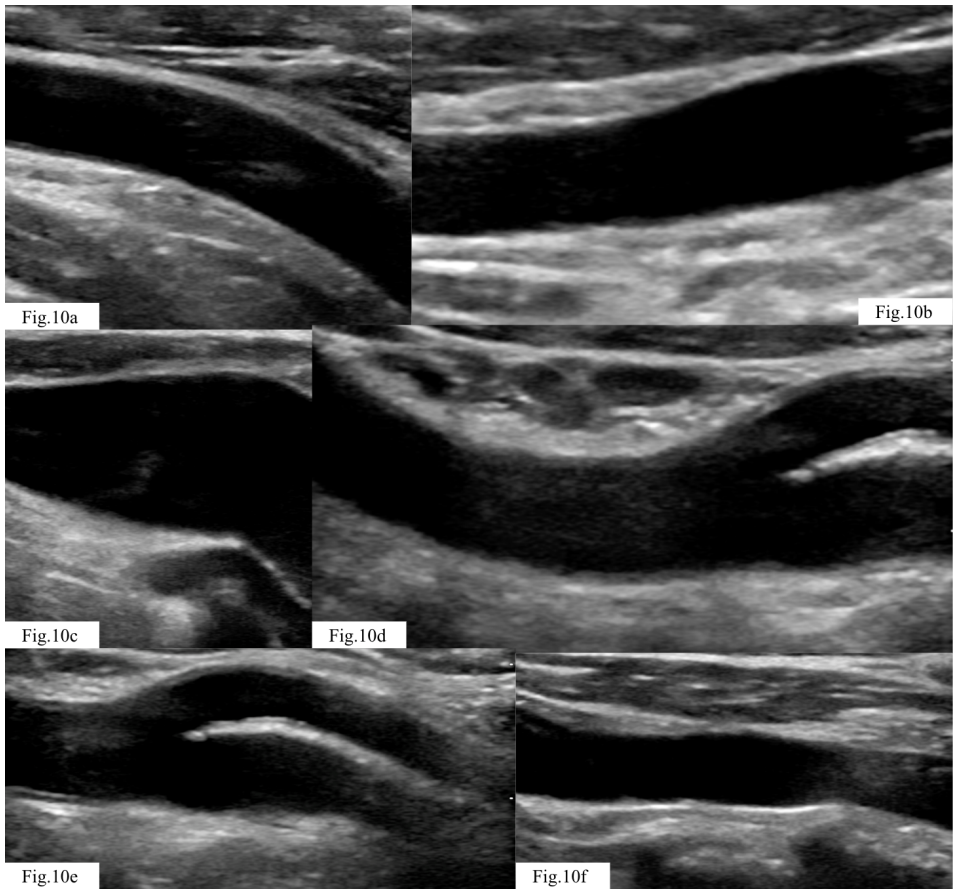


Fig. 10. Structural and hemodynamic alterations in the 36–45-year age group
Picture taken by the authors

metabolic load increasingly affects endothelial and renal microcixrculation [23, 24]. This "metabolic adaptation" phenotype reflects effective interorgan regulation and balanced redox status, representing a model of healthy early aging. In the majority of participants in the 3-rd group, minimal echogenicity had no clinical or biochemical significance, indicating compensatory metabolic adaptation. Age-related ultrasound patterns are presented in Supplementary Materials: Fig. 1a–j (18–26 years), Fig. 2a–h (27–35 years), Fig. 3a–h (36–45 years).

Table 1. Age-related Ultrasound results

Parameters	Group 1 (18–26 yrs, n=68)	Group 2 (27–35 yrs, n=70)	Group 3 (36–45 yrs, n=50)	p G1 vs G2	p G2 vs G3	p G1 vs G3
Kidney Patterns						
Length, cm	10.5 ± 0.8	11.2 ± 0.6	11.0 ± 0.7	<0.001	0.105	<0.001
Width, cm	5.3 ± 0.3	5.6 ± 0.3	5.8 ± 0.3	<0.001	<0.001	<0.001
Parenchymal thickness, mm	18.5 ± 2.5	19.2 ± 3.8	21.5 ± 2.5	0.202	<0.001	<0.001
Increased echogenicity, %	0	28	35	<0.001	0.430	<0.001
Ultrasound findings of the internal jugular vein / common carotid artery						
CIMT, mm	0.48 ± 0.05	0.62 ± 0.08	0.72 ± 0.09	<0.001	<0.001	<0.001
Arterial diameter, mm	6.6 ± 0.5	6.9 ± 0.5	7.1 ± 0.5	<0.001	0.033	<0.001
Peak velocity, cm/s	50 ± 5	75 ± 5	87 ± 2	<0.001	<0.001	<0.001
Mean velocity, cm/s	8.2 ± 0.8	6.5 ± 0.5	6.5 ± 0.7	<0.001	1.000	<0.001
Additional findings	No stenosis or plaques	Early jugular wall masses; minimal stenosis (5–15%)	Stenosis up to 25%, plaques; flow 0.1–0.3 L/min	—	—	—
Echocardiographic data						
LVEDD, cm	4.7 ± 0.3	4.8 ± 0.3	4.9 ± 0.4	0.052	0.139	0.004
LVESD, cm	3.0 ± 0.2	3.1 ± 0.3	3.2 ± 0.3	0.023	0.075	<0.001
IVSd, cm	0.85 ± 0.08	0.95 ± 0.08	0.98 ± 0.10	<0.001	0.082	<0.001
LVPWd, cm	0.85 ± 0.08	0.95 ± 0.08	0.98 ± 0.10	<0.001	0.082	<0.001
Ejection fraction (EF), %	66 ± 2	64 ± 3	63 ± 3	<0.001	0.075	<0.001
Left atrium (LA), cm	3.1 ± 0.2	3.3 ± 0.3	3.4 ± 0.3	<0.001	0.075	<0.001
E/A ratio	2.1 ± 0.3	1.9 ± 0.3	1.7 ± 0.4	<0.001	0.004	<0.001
E/e' ratio	6.3 ± 0.8	6.8 ± 1.0	7.2 ± 1.2	0.002	0.057	<0.001
Thyroid Patterns						
Normal structure, %	94.1	32.9	6	<0.001	0.003	<0.001
Diffuse hypoechogenicity, %	0	41.1	8	<0.001	<0.001	0.030
Small nodules ≤5 mm, %	5.9	18.9	24	0.036	0.501	0.006
Cysts, %	0	0	6	1.000	0.070	0.073

Source: compiled by the authors of this study

Thus, data highlight liver echogenicity as an early marker of metabolic dysregulation preceding biochemical abnormalities and underscore the value of integrating imaging with anthropometric and laboratory assessments for timely preventive interventions.

KIDNEYS — PRECLINICAL CHANGES IN PARENCHYMA AND MICROVASCULATURE

Preclinical parenchymal and microvascular kidney changes are increasingly recognized as early markers of future nephropathy [16, 25]. In our cohort, all functional indicators were within reference ranges (Supplementary Materials) despite structural ultrasound variations. Average kidney size corresponded to physiological norms across age groups, with age-related morphometric and echogenic features (Table 1).

In the 1st group, kidney size parameters indicated preserved nephron and microvascular integrity, supporting effective perfusion and filtration. Mild parenchymal thickening (2–3 mm) in some participants likely reflected benign anatomical variability, including increased mesangial volume and endothelial proliferative changes not detected by laboratory tests. **In the 2nd group,** increased parenchymal echogenicity was observed in 28% of participants, indicating early preclinical microvascular alterations [26]. Within our proposed model, these findings may represent an early marker of systemic endothelial stress, remaining clinically silent and without laboratory abnormalities. The ultrasound features suggest mild, compensated glomerular and tubular dysfunction supported by intact nephrons and adaptive mechanisms [27]. **In the 3rd group,** 35% demonstrated increased echogenicity,

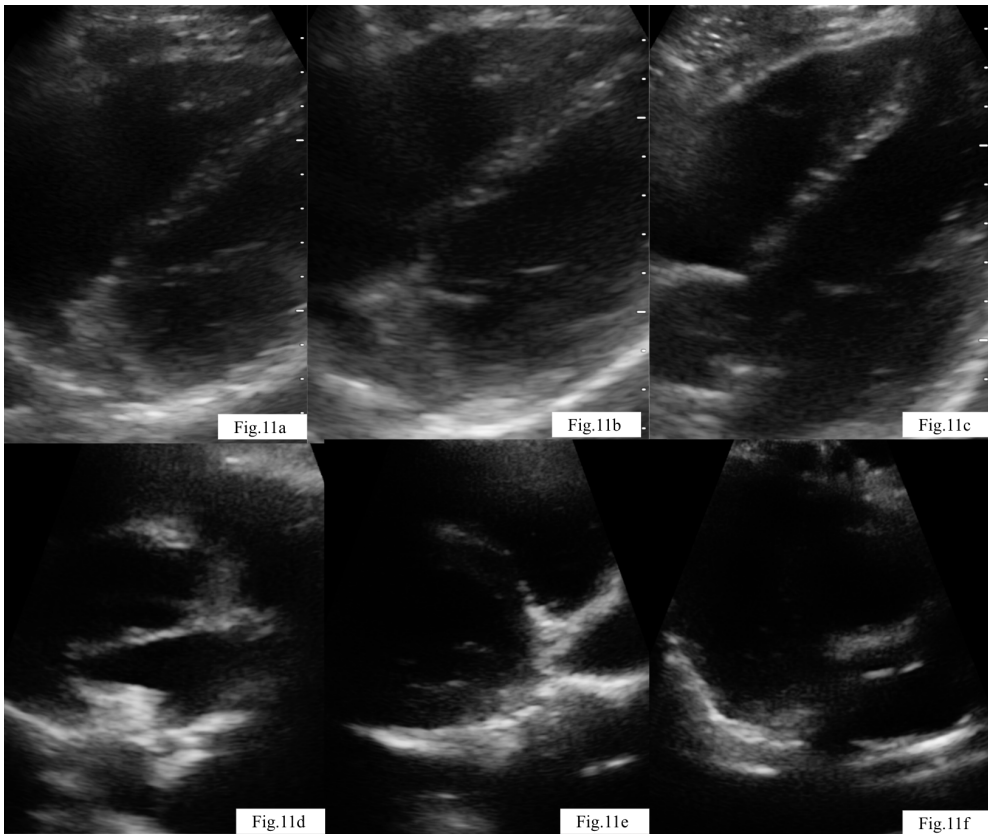


Fig. 11. Echocardiographic profile of young adults
Picture taken by the authors

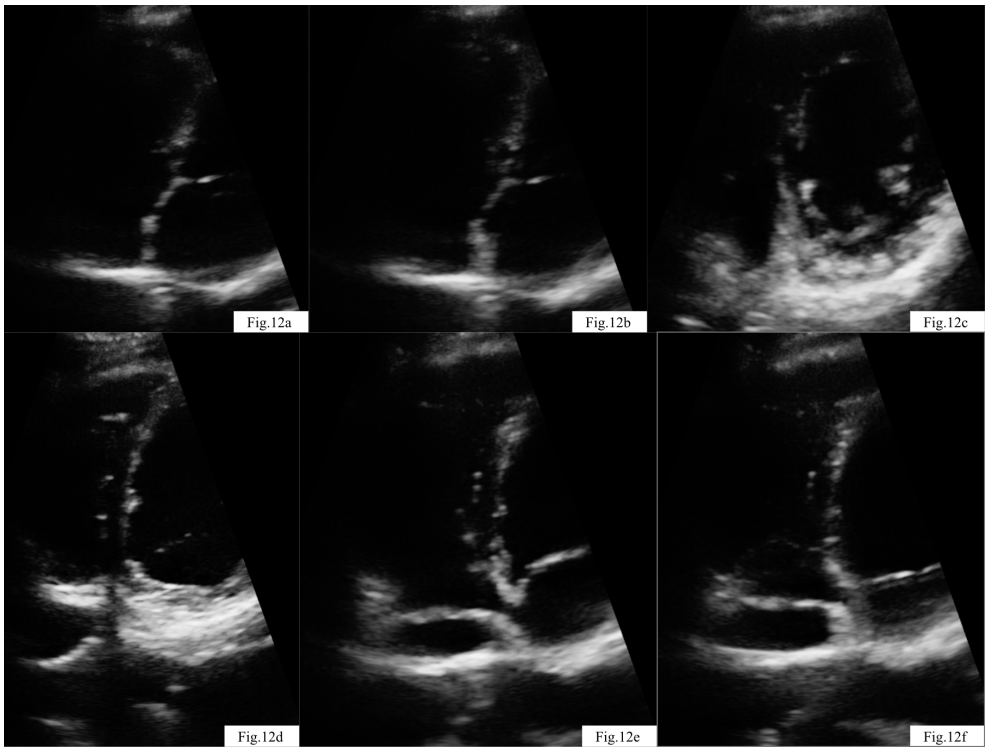


Fig. 12. Echocardiographic parameters in adults aged 27–35 demonstrating preserved functional stability and normal early diastolic filling
Picture taken by the authors

consistent with progressive mesangial and interstitial changes and subtle perfusion disturbances preceding overt nephropathy. Age-related ultrasound patterns are shown in Supplementary Materials: Fig. 4a–h (18–26 years), Fig. 5a–f (27–35 years), Fig. 6a–i (36–45 years).

***Arteria carotis and vena jugularis* — markers of endothelial dysfunction.** Ultrasound examination of the common carotid artery and internal jugular vein in 188 young adults revealed early markers of endothelial dysfunction. Mean CIMT was 0.58±0.07 mm, with 22.6% of patients exceeding the 75th percentile for age and sex. Two individuals showed bilateral focal intimal thickenings (up to 1.15 - 1.18 mm), surpassing the recommended 0.9 mm limit. These findings we consider as

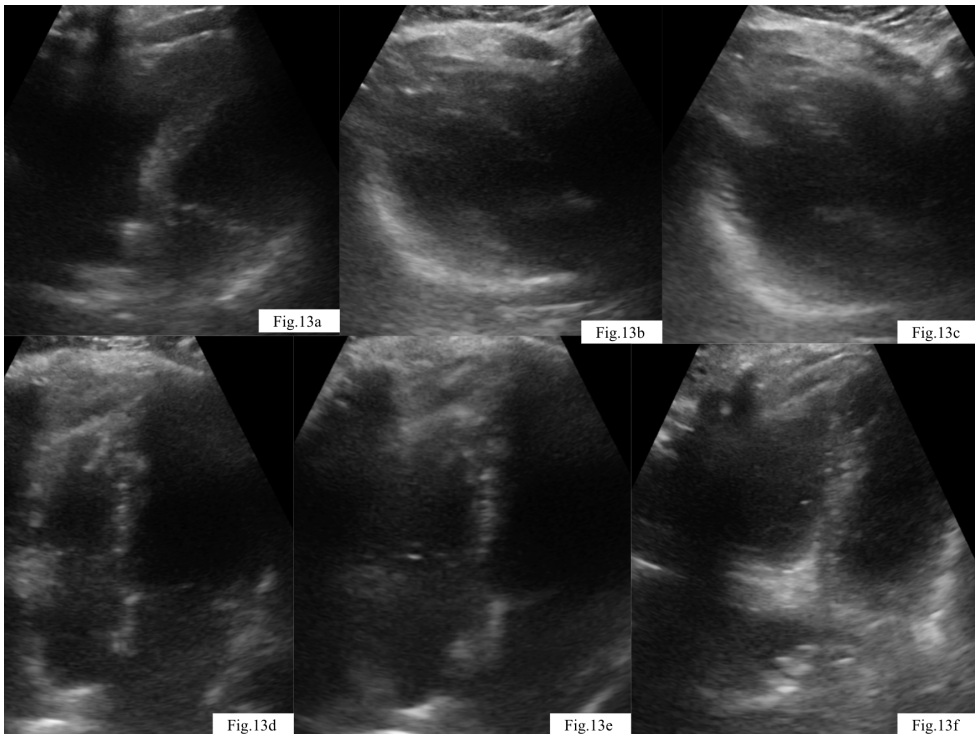


Fig. 13. Echocardiographic parameters in adults aged 36–45 showing normal cardiac function without signs of dysfunction
Picture taken by the authors

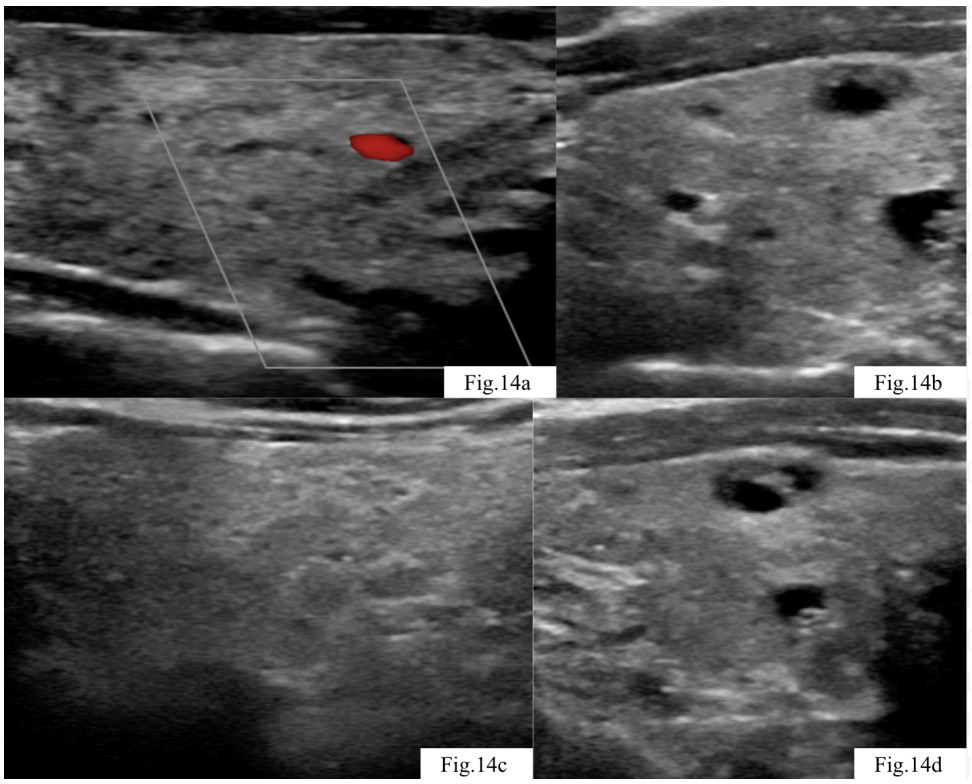


Fig. 14. Ultrasonographic patterns of the thyroid gland in clinically and laboratory 'healthy' young adults
Picture taken by the authors

early morphological predictors of vascular remodeling [11]. CIMT correlated significantly with BMI ($\rho = 0.41$; $p < 0.001$), waist circumference ($\rho = 0.44$; $p < 0.001$), and systolic blood pressure ($\rho = 0.36$; $p < 0.01$), which corresponds to the findings of our previous studies and underscores the contribution of metabolic risk factors to early arterial changes. CIMT was selected as the primary vascular parameter given its established validity as a surrogate marker for subclinical atherosclerosis and its demonstrated correlation with metabolic risk factors in young adults.

In the 1-st group all vascular parameters remained within physiological norms, with no plaques or stenosis, indicating preserved endothelial function (Table 1). This allows considering this group as a control phenotype with fully preserved endothelial function. **In the 2nd group,** early structural changes were observed (Table 1), including CIMT elevation in 13 participants, early

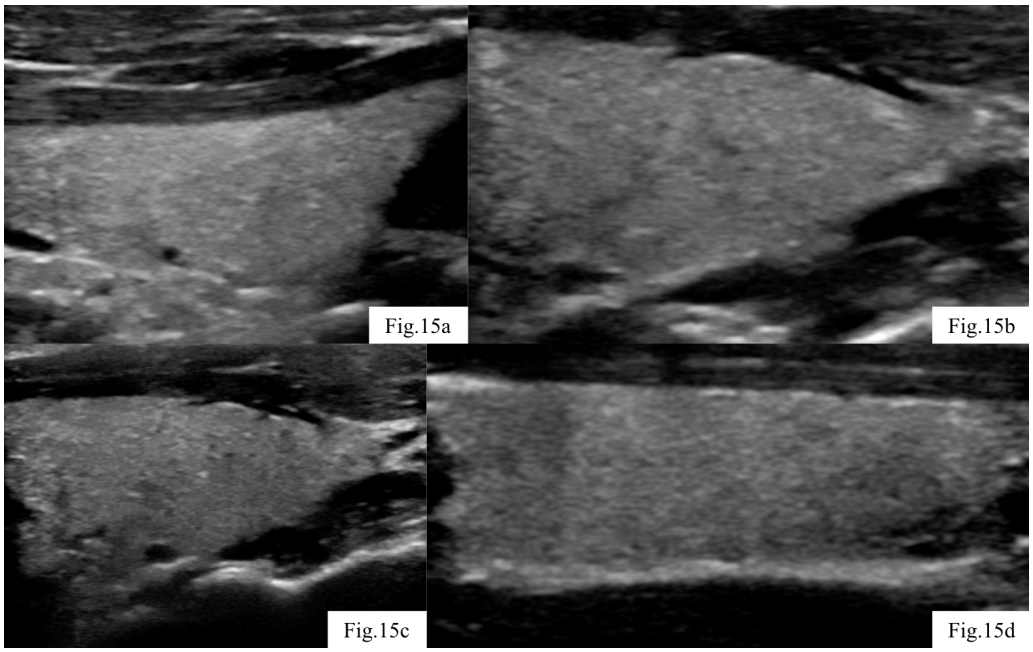


Fig. 15. Ultrasonographic patterns in adults aged 18–26
Picture taken by the authors

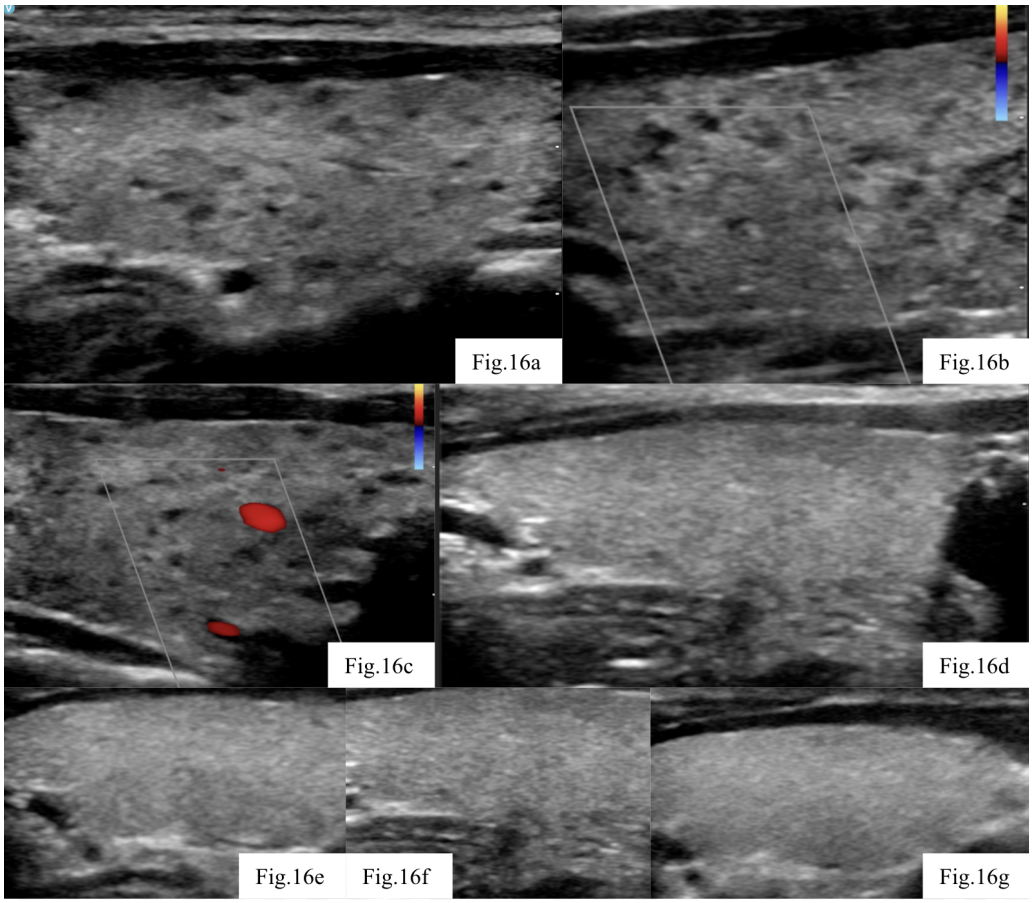


Fig. 16. Ultrasonographic patterns in adults aged 27–35
Picture taken by the authors

jugular wall masses, and minimal hemodynamically insignificant stenosis (<25%). These findings indicate that plaque formation can be detected at an early, preclinical stage. Hemodynamically, this group showed a moderate increase in peak blood flow velocity (up to 70–80 cm/s) and a decrease in mean velocity (6–7 cm/s), suggesting increased vascular wall stiffness [28,29]. In some patients, minimal stenosis (5–15%) and small echogenic areas were also noted. **In the 3-rd group ,** the average CIMT value was higher, plaques and stenoses up to 25% were detected, and peak blood flow velocities approached 85–89 cm/s, while the mean velocity remained at 6–7 cm/s (Table 1), reflecting reduced arterial elasticity and early hemodynamic disturbance. The volumetric blood flow in this group demonstrated the greatest variability, from 0.1 to 0.3 L/min. Age-re-

lated ultrasound data are presented in Supplementary Materials: Fig. 7a–d, Fig. 8a–c, Fig. 9 a–f, Fig. 10 a–f.

Combined morphometric and hemodynamic ultrasound parameters enable sensitive detection of subclinical endothelial dysfunction, reflecting early inflammatory remodeling and loss of vascular elasticity [30]. Carotid and jugular vessels thus serve as early biomarkers of preclinical atherogenesis in young adults, allowing identification of vascular changes before clinical or laboratory signs appear, as also noted by Jones DL et al. [30]. Detection of an atherogenic mass in a group-2 patient underscores the need for regular preventive ultrasound monitoring.

Heart — early echocardiographic changes. Across all age groups, cardiac chamber dimensions and functional indices remained within physiological limits, with no evidence of dilation, hypertrophy, remodeling, or systolic/diastolic dysfunction; NT-proBNP levels were well below pathological thresholds. Detailed data are provided in Supplementary Materials Table 2.

In the 1st group, echocardiographic parameters reflected optimal myocardial elasticity and reserve. **The 2nd group** maintained comparable functional stability without signs of impaired early diastolic filling. Similarly, **the 3rd group** showed no abnormalities, with all parameters remaining within normal limits (Table 1). Age-related ultrasound patterns are presented in Supplementary Materials Fig. 11a–f (18–26 years), Fig. 12a–f (27–35 years), and Fig. 13a–f (36–45 years).

Overall, all cohorts demonstrated a stable diastolic profile and preserved cardiovascular homeostasis. Nevertheless, reports of increasing early-onset cardiac pathology in young adults [31] emphasize the role of echocardiography in early risk stratification and prevention.

The thyroid gland — markers of hidden endocrine dysfunctions. Thyroid ultrasound evaluation revealed two main preclinical phenotypes in a cohort of 188 clinically healthy adults: minimal diffuse echostructural changes (47.35%) and small ≤5 mm iso- or hypoechoic nodules (7.44%) (Fig.14). Simple colloid cysts were found in 4.3% of participants. All nodular findings corresponded to benign patterns requiring periodic follow-up [17].

In the 1st age group, almost all scans showed normal echostructure, with only minor variants and no laboratory abnormalities (Table 1). This reflects the physiological state of young age with stable hormonal and neuro-immune balance. **In the 2nd group,** Hashimoto-like features were more frequent, mainly diffuse hypoechogenicity and small nodules. The predominant phenotype was diffuse hypoechogenicity, sometimes with nodules up to 5 mm; isolated small nodules were less common, and cystic formations were rare (Table 1). These changes indicate early inflammatory activity and initial thyroid remodeling [17]. The nodules typically appeared iso- or hypoechoic with thin peripheral vascularization, indicating active tissue remodeling [17, 32]. Clinically, this pattern is associated with a higher likelihood of emerging antibodies and progressive autoimmune involvement [17, 32], making regular ultrasound and antibody monitoring advisable for this age group. **In the 3-rd group,** the ultrasound pattern demonstrated considerable variability (Table 1). Most participants had a normal thyroid pattern, while others demonstrated small nodules (≤5 mm) or minimal parenchymal alterations without significant hypoechogenicity or fibrosis. Some presented with early diffuse heterogeneity or simple cystic formations. Nodules classified as benign by EU-TIRADS (10%) required only routine follow-up. Vascularization was normal, with no clinical or laboratory signs of thyroid dysfunction. Participants with suspicious ultrasound features (14%) were referred for specialist evaluation despite normal thyroid function. Age-related ultrasound data are presented in Supplementary Materials: Fig. 15 (18–26 years), Fig. 16 (27–35 years), Fig. 17 (36–45 years).

Our analysis indicates that thyroid diffuse hypoechogenicity reflects early morphological changes of autoimmune thyroiditis, including mild lymphocytic infiltration, follicular loss, and colloid disruption. These changes likely result from Th1/Th17 activation, impaired T-regulatory function, local cytokine production (IL-6, IFN-γ, TNF-α), and B-cell autoantibodies [17, 32]. Ultrasound hypoechogenicity usually precedes changes in TSH, free T4, or antibody levels and is therefore an early sensitive marker, while serological abnormalities appear later [17, 32].

The comprehensive "ultrasound risk phenotype" and the LUMINA System. By integrating the results of our 11 sub-studies [11-16, 33-35, 37,38] we developed a unified system of early multi-organ stratification of subclinical risk — the LUMINA System (Ultrasound Multi-Organ Risk Stratification), which is based on the principle of a single pathological continuum, within which minimal structural deviations in different organs reflect early phases of metabolic, microvascular, and immuno-endocrine remodeling. The system integrates ultrasound findings of the liver, kidneys, heart, carotid arteries, and thyroid into a single indicator of preclinical systemic–metabolic risk, reflecting early structural and functional changes. Only 20.2% (n = 38) of participants showed no subclinical abnormalities, whereas 79.8% (n = 150) had ultrasound markers of early systemic disturbances, including multi-organ involvement in 48.9% (n = 92) and three or more markers in 21.8% (n = 41). Early changes predominantly affected the liver, kidneys, ves-

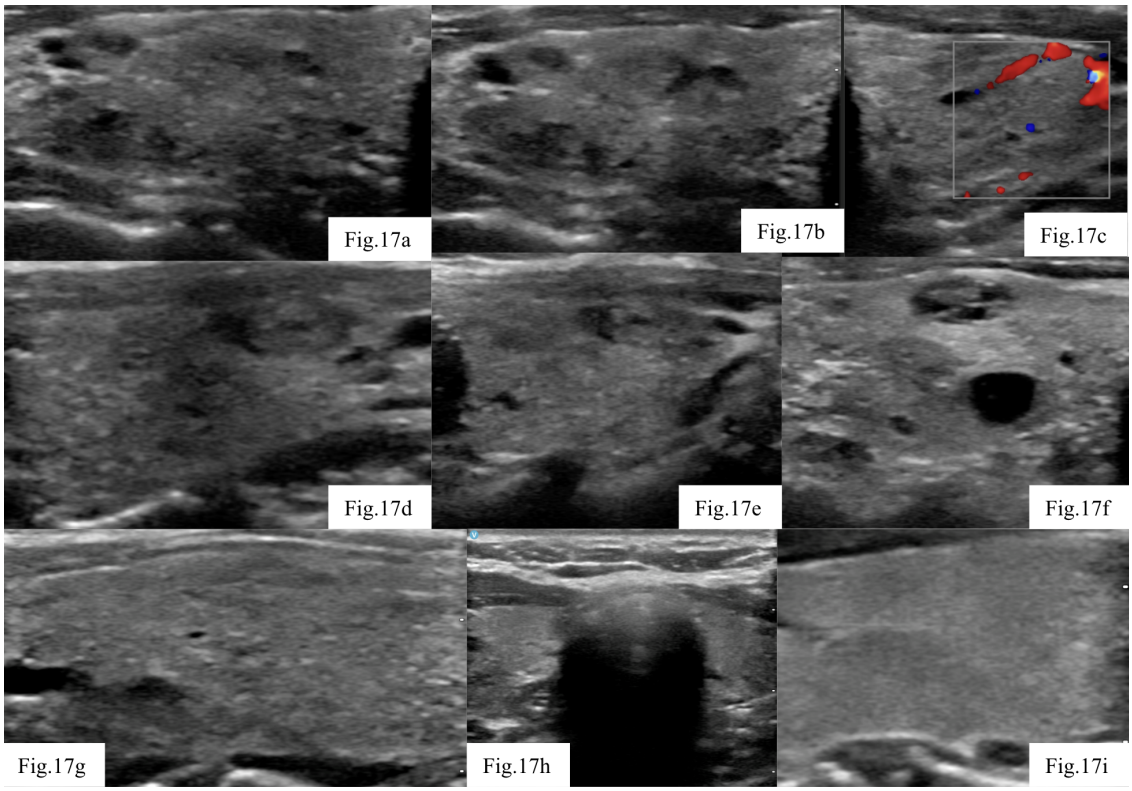


Fig. 17. Ultrasonographic patterns in adults aged 36–45
Picture taken by the authors

sels, and thyroid, while cardiac involvement was absent, suggesting a later onset. The coexistence of metabolic, microvascular, endothelial, and endocrine alterations at the preclinical stage highlights early multi-organ risk. Thus, the integrated ultrasound phenotype serves as a sensitive marker of systemic stress, preceding biochemical and clinical manifestations and enabling early prevention. The LUMINA System includes five domains:

1. **The hepatic domain** serves as an early marker of metabolic load: focal heterogeneity and mild echogenicity increase suggest steatogenic changes, while diffuse echogenicity reflects insulin resistance. Combined with BMI and waist circumference, these patterns represent the core axis of metabolic stress.
2. **The renal domain** captures early parenchymal remodeling associated with metabolic dysfunction. Increased echogenicity, reduced cortico-medullary differentiation, microcystic or echo-negative inclusions indicate initial structural changes, whereas minor size asymmetry reflects adaptation; renal size is considered a risk factor rather than a diagnostic criterion.
3. **The vascular domain** reflects early atherogenesis, including intima–media thickness above the 75th percentile, focal non-stenotic thickening, increased wall stiffness or heterogeneity, and isolated hyperechoic inclusions, consistent with endothelial dysfunction and reduced elasticity.
4. **The cardiac domain** includes subtle echocardiographic changes: early LV wall thickening, mild LV dilation within normal limits, minimal physiological regurgitation, and slightly increased myocardial echogenicity.
5. **The thyroid domain** reflects early immuno-endocrine remodeling, with diffuse hypoechogenicity or heterogeneity indicating initial autoimmune activity, small nodules (<10 mm) early proliferation, gland enlargement compensatory response, and moderately increased vascularization.

All five domains are evaluated using four unified criteria forming an integral subclinical risk scale. Table 3 summarizes organ-specific criteria (liver, kidneys, carotid arteries, heart, thyroid), each scored 1–2 points. The total score defines four risk levels: 0–4 low, 5–11 moderate, 12–20 high, 21–29 very high. This system standardizes multi-organ subclinical assessment and guides further monitoring or intervention. The LUMINA System, through its unified multi-organ structure, allows early detection of potentially reversible pathological phenotypes in young adults, supports personalized risk correction, and forms a basis for standardized preclinical monitoring.

MOLECULAR–BIOCHEMICAL PANEL: AN EMPIRICAL–MECHANISTIC MODEL OF THE MOLECULAR–IMAGING CONTINUUM

The molecular–biochemical panel is presented separately as a hypothetical tool requiring validation in larger cohorts. Early morphological changes may reflect underlying metabolic–immune remodeling. In a small

Table2. Baseline characteristics of the study cohort (N = 188)

Category	Parameter	Mean ± SD / %		
Demographics	Age, years	31.8 ± 6.7		
	Male sex, %	46.3		
	Female sex, %	53.7		
Anthropometry	Body mass index, kg/m²	18–26 years	27–35 years	36–45 years
	p< 0.05	23.1 ± 3.2	31.8 ± 6.1	25.0 ± 0.6
	Waist circumference, cm male female		 85.1 ± 11.4 79.2 ± 10.5	
	Waist-to-hip ratio male female		 0.90 ± 0.07 0.81 ± 0.07	
Hemodynamics	Systolic blood pressure, mmHg	122.3 ± 11.4		
	Diastolic blood pressure, mmHg	78.1 ± 8.6		
	Heart rate, bpm	74 ± 9		
Biochemistry	Fasting glucose, mmol/L	5.1 ± 0.6		
	Fasting insulin, μU/mL	11.2 ± 3.7		
	HOMA-IR	2.4 ± 0.9		
	Total cholesterol (TC), mmol/L	5.7 ± 0.8		
	HDL-C, mmol/L	Female	Male	
		1.05 ± 0.15	0.89 ± 0.12	
	LDL-C, mmol/L	3.3 ± 0.7		
	Triglycerides (TG), mmol/L	1.6 ± 0.5		
	Atherogenic index (TC/HDL-C)	3.8		
	Creatinine, μmol/L	82 ± 12		
	ALT, U/L	22 ± 9		
	AST, U/L	20 ± 6		
	creatinine, μmol/L	78.4±12.6		
	urea, mmol/L	5.2±0.9		
	serum albumin, g/L	42.3±3.1		
	Glomerular filtration rate (GFR), mL/min/1.73 m²	96.8±8.4		
urinary test	microalbuminuria, mg/L,	18.2±6.4		
	urine protein, g/day.	0.08±0.03		
	urine creatinine, mg/dl	99.3±55		
	albumin-to-creatinine ratio (ACR), mg/mmol	2.07±0.87		
Lifestyle factors	Regular physical activity, %	64		
	Daily fruits and vegetables, %	58		
Ultrasound examination of the arteria carotis communis and vena jugularis	CIMT, mm	0.58 ± 0.07		
Cardiac Structural and Functional Parameters	LVEDD, cm	4.8 ± 0.4		
	LVESD, cm	3.1 ± 0.3		
	IVSd, cm	0.9 ± 0.1		
	LVPWd, cm	0.9 ± 0.1		
	Ejection fraction (EF), %	64 ± 3		
	Left atrium (LA), cm	3.3 ± 0.3		
	E/A ratio	1.9 ± 0.4		
	E/e' ratio	6.8 ± 1.2		
	NT-proBNP, pg/mL	42.5 ± 14.3		
Thyroid gland	Minimal diffuse echostructural changes, %	47.35		
	Small iso-/hypoechoic nodules ≤5 mm, %	7.44		
	Simple cysts, %	4.3		

Source: compiled by the authors of this study

Table 3. LUMINA System: Integrated risk assessment & Scoring

Organ specific changes and scoring		
Organ	Finding / Description	Score
Liver	Local heterogeneity / minimal echogenicity	1
	Diffuse changes (Marked increase in echogenicity)	2
	BMI ≥25 kg/m^2	1
	Waist circumference >90/80 cm	2
Kidneys	Increased Echogenicity	2
	Partial reduction of cortico-medullary differentiation	1
	Local changes (Microcysts / echonegative areas)	1
	Size (Mild asymmetry)	1
Carotid arteries	CIMT >75 percentile	2
	Focal Thickening, without stenosis	1
	Wall Stiffness / heterogeneity	2
	Findings (Hyperechoic foci)	1
Heart	Local LV wall thickening	2
	LV at the upper limit of normal	1
	Valves (Minimal regurgitation)	1
	Increased echogenicity of Myocardium	2
Thyroid gland	Echotexture (Hypoechogenicity / heterogeneity)	1
	Nodules ≤10 mm	1
	Volume >18/25 ml	2
	Doppler (Increased vascularization)	2
Total Score & Risk Interpretation		
Total score	Risk level	Interpretation
0–4	Low	Preclinical changes are minimal or absent.
5–11	Moderate	Subclinical changes in 1–2 organs; monitoring is recommended.
12–20	High	Multi-organ changes; active risk correction is required.
21–29	Very high	Early systemic dysfunctions; multidisciplinary management required.

\Source: compiled by the authors of this study

subgroup, ApoB (n=3, 1.15 ± 0.26 g/L), TNF-α (n=24, 3.87 ± 0.96 pg/mL), and IL-6 (n=24, 12.25 ± 2.23 pg/mL) were assessed. Although the data are insufficient for statistically robust conclusions, they indicate a tendency toward elevated cytokines and atherogenic particles, consistent with previous studies [35, 36]. The model is based on the following mechanisms: ApoB reflects atherogenic particles and affects the intima–media complex [37]; TNF-α increases vascular tone and contributes to microvascular injury [38, 39]; IL-6 coordinates low-grade inflammation and metabolic integration [40]. These findings remain preliminary and require validation in larger, dynamically monitored cohorts.

An age-stratified analysis of subclinical risk using the LUMINA system was conducted based on quantitative ultrasound assessment of five organ systems (liver, kidneys, carotid arteries, heart, thyroid), with a maximum score of 29 points.

In the 18–26 yrs cohort, the mean LUMINA score was 0.44 ± 0.31, representing a reference phenotype, with 94% showing no structural abnormalities. Only minimal thyroid changes (1 point in 5.9%) were observed, while all other domains remained within physiological limits. **The 27–35 yrs group** demonstrated a marked shift toward multisystem involvement, with a mean score of 12.12 ± 3.68, significantly higher than in the youngest cohort ($p < 0.001$); 87% fell into high or very high risk categories. Liver and thyroid domains contributed most to the burden, alongside vascular remodeling and moderate renal changes, while cardiac function remained preserved. The LUMINA index correlated with BMI, waist circumference,

Table 4. Core LUMINA Risk Metrics Across Age Cohorts

Metric	18–26 yrs (n = 68)	27–35 yrs (n = 70)	36–45 yrs (n = 50)	p between groups (G1 vs G2 vs G3)
Mean LUMINA score	0.44 ± 0.31	12.12 ± 3.68	8.67 ± 2.80	<0.0001
Risk category	Very Low / Reference	High / Very High	Moderate / High	—
BMI (kg/m^2)	23.1 ± 3.2	31.8 ± 6.1	25.2 ± 2.8	<0.0001
Liver score	0	3.71 ± 0.26	0.96 ± 0.15	<0.0001
Renal score	0	1.39 ± 0.20	1.74 ± 0.24	<0.0001
Vascular score	0	3.61 ± 0.37	4.16 ± 0.41	<0.0001
Cardiac score	0	0	0	0 in all groups
Thyroid score	0–1	3.41 ± 0.30	1.81 ± 0.38	—

Source: compiled by the authors of this study

and HOMA-IR (all p < 0.01). **In the 36–45 yrs cohort,** the mean score decreased to 8.67 ± 2.80, indicating a metabolic adaptation phenotype. Hepatic burden declined, whereas vascular remodeling and renal involvement increased; cardiac parameters remained normal and thyroid changes moderate. These data are summarized in Table 4.

DISCUSSION

This study shows that a high proportion of clinically healthy young adults exhibit subclinical multi-organ structural changes detectable by ultrasound despite normal laboratory findings. These data indicate that early metabolic, microvascular, endothelial, and immuno-endocrine remodeling develops long before clinical disease and remains largely invisible to conventional risk assessment models.

The distribution of ultrasound findings suggests an age-dependent and organ-specific continuum. Increased liver echogenicity predominated in early adulthood and correlated with anthropometric and insulin-resistance markers, supporting the role of the liver as an early indicator of systemic metabolic stress. Greber-Platzer et al. (2019) arrived at similar conclusions. [41] They found that increased liver echogenicity predominated in adolescents aged 14–18 years (49% among those with pathological echogenicity vs. 34% with normal echogenicity, P < 0.0001) and correlated with anthropometric markers, particularly extreme obesity (OR = 3.45, 95% CI: 1.9–6.1, P < 0.0001) and elevated BMI (34.0 ± 6.2 kg/m^2 vs. 31.2 ± 5.9 kg/m^2, P < 0.0001). [41] Furthermore, the authors confirmed a significant association between increased liver echogenicity and insulin resistance markers: impaired glucose metabolism was associated with elevated liver enzymes > 50 U/L (OR = 4.4, 95% CI: 1.6–11.8, P < 0.005). [41] The researchers emphasized that NAFLD serves as an early mediator of metabolic disturbance, supporting the role of the liver as an early indicator of systemic metabolic stress in obese youth. [41] With increasing age, renal parenchymal echogenicity and carotid vascular remodeling became more prevalent, reflecting a shift toward microvascular and endothelial involvement. These findings align with our conclusions. Siddappa et al. (2013) reported consistent findings regarding progressive parenchymal changes. [42] They demonstrated that increased renal cortical echogenicity correlated with disease progression (P = 0.004), with echogenicity representing irreversible structural damage. [42] The authors cited evidence that renal echogenicity has the strongest correlation with histologic parameters including glomerular sclerosis, tubular atrophy, interstitial fibrosis, and interstitial inflammation, supporting the concept that increasing echogenicity reflects underlying microvascular and tissue involvement in chronic disease. [42] Thyroid hypoechogenicity, particularly in the 27–35-year group, occurred in the absence of hormonal abnormalities and likely represents early immune-mediated tissue remodeling. These findings are consistent with our observations. Vejbjerg et al. (2006) demonstrated in a large cross-sectional study of 4,649 randomly selected adults that thyroid hypoechogenicity occurs as an early sign of thyroid dysfunction even in subjects without overt thyroid disease. [43] Participants with decreased echogenicity had a higher mean TSH (1.65 mU/l) compared with subjects with normal echogenicity (1.21 mU/l, P<0.0001), with this association being stronger in subjects with markedly decreased echogenicity (4.20 mU/l, P<0.0001). [43] Importantly, subjects with decreased echogenicity had a higher risk of having thyroid autoantibodies than subjects without decreased echogenicity (P<0.0001), and this association was stronger when echogenicity was markedly decreased. [43] The authors concluded

that decreased echogenicity and irregular echo pattern represent early markers of thyroid dysfunction, supporting the concept that structural tissue changes reflect immune-mediated remodeling occurring before the development of overt hormonal abnormalities. [43]

Integration of these findings into the LUMINA system revealed a non-linear risk pattern, with the highest burden of subclinical alterations in the 27–35-year cohort and partial redistribution of organ involvement thereafter. This suggests a critical window in early adulthood characterized by maximal phenotypic instability, during which structural changes may still be modifiable. The absence of cardiac involvement across cohorts is consistent with later myocardial engagement in the pathological cascade and supports the value of upstream detection. Clinically, these results underscore the limitations of laboratory-based and short-term risk models in young adults. Systemic ultrasound phenotyping provides a practical, non-invasive method for identifying discordance between structural remodeling and biochemical normality, enabling earlier individualized prevention. The study is limited by its single-center design, sample size, and observational nature, and the molecular biomarker data remain exploratory. Longitudinal studies are required to validate the prognostic significance of the LUMINA score.

CONCLUSIONS

Systemic multi-organ ultrasound phenotyping of young adults enables the detection of subclinical structural and functional changes in the liver, kidneys, vessels, and thyroid gland even in the absence of laboratory and clinical abnormalities. Since individuals in this age group rarely undergo preventive examinations, such changes often remain undetected until clinically manifest pathology develops. The identification of a universal "ultrasound risk phenotype" supports the rationale for implementing preventive ultrasound screening in young adults and opens opportunities for proactive metaphylaxis, personalized prevention, and the advancement of preventive medicine.

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A complete list of references can be requested from the authors.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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