Supplementary tables

Table S1. Shared differentially expressed molecules across multiple diseases. Only molecules with literature supports to be associated with multiple diseases were listed.

Type	Name	Summary	Relevant diseases
Protein	AFAM	Highly expressed in group b,c,d,e,g	MTS [1, 2]
	MASP1	Highly expressed in group b, d, f	Prediabetes [3], Obesity, Hyperlipidemia [4]
Metabolites	glycine	Lowly expressed in group b,c,d,f	T2D [5], obesity [6], MTS [7], Hyperlipidemia [8]
	SM(d16:0/20:0)+H	Highly expressed in group c, f, g	Insulin resistance, MTS [9]
	Cer	Highly expressed in group cand f	Insulin resistance, diabetes [10, 11]
	FFA FFA 18:4	Highly expressed in group c, d, g	Insulin resistance, MTS [12]
Source proteins of the polypeptides	ALBU	Highly expressed in group c,d,f,g	MTS [13], T2D [14, 15], Obesity [16], Hyperlipidemia [17]
	ITIH4	Lowly expressed in group c, e, f	Metabolically healthy obesity [18, 19]
	APOA1	Lowly expressed in group b, c, f	MTS [20], T2D[21], Hyperlipidemia

Table S2. Disease specific differentially expressed molecules. Only molecules with literature supports to be associated with the specific disease were listed.

Disease	Molecular type	Molecule	References
Obesity	Protein	CAMP	[22]
		IGLC2 /IGLC6	[23]
	Metabolite	epinephrine	[24]
		C0−carnitine	[25]
		Hypoxanthine	[26]
		L−proline	[27]
		Pyruvic acid	[28]
	Polypeptide source protein	IGHG1	[23]
		FETUA	[29]
		FIBA	[30]
MTS	Protein	APOC2	[31]
		RET4	[32]
	Metabolites	TG	
		DG	[33]
		FFA	[12]
		CDCA	[34, 35]
	Polypeptide source protein	FIBA	[36]
		CO3	[37]
		A1AT	[38]
Hyperglycemia	Protein	CADH5	[39]
		CBG	[40]
		FIBA	[41, 42]
		GPV	[43]
	Metabolites	Ethanolamine	[44]
		Serine	[45]
	Polypeptide source protein	FIBA	[41, 42]
		TRFE	[46]
		CO3	[47]
		IGKC	[48]
Hypertension	Metabolites	Carnitine	[49]
		Indoxyl sulfate	[50]
	Polypeptide source protein	FIBA	[51, 52]
		ALBU	[53-55]
Hyperlipidemia	Protein	LBP	[56, 57]
		FIBA	[58]
		CO3	[59]
T2D	Protein	CAH1	[60]
	Metabolites	PC(20:1/22:6)+H	[61]
		KNG1	[62]
		MYEF2	[63]

Table S3. The peptides corresponding to the abbreviated peptide names in Figure 6.

Node name	Peptide
A1AT-pp1	EDPQGDAAQKTD
A1AT-pp2	EDPQGDAAQKTDTS
A1AT-pp3	EDPQGDAAQKTDTSHHD
A1AT-pp4	EDPQGDAAQKTDTSHHDQD
AACT-pp1	HPNSPLDEENLTQENQD
ALBU-pp1	DAHKSEVAHRF
ALBU-pp2	DAHKSEVAHRFKDLG
ALBU-pp3	HKSEVAHRFKDLG
AMBP-pp3	GDEELLRFS
APOA1-pp1	DEPPQSPWD
APOA1-pp2	EEYTKKLNTQ
APOA1-pp3	LSALEEYTKKLNTQ
APOL1-pp1	EEAGARVQQNVPSGTD
APOL1-pp2	EEAGARVQQNVPSGTDTGD
CO3-pp1	SEETKENEGFTVTAEGK
CXCL7-pp1	NLAKGKEESLDSD
FETUA-pp1	APHGPGLIYRQPN
FIBA-pp1	ADSGEGDFLAEGGGV
FIBA-pp2	FTSSTSYNRGDST
FIBA-pp3	FTSSTSYNRGDSTFESKSYKMA
FIBA-pp4	KMADEAGSEADHEGTHST
FIBA-pp5	NRGDSTFESKSY
FIBA-pp6	SSYSKQFTSSTSYNRGDSTFESKS
FIBA-pp7	STSYNRGDSTFES
FIBA-pp8	SSYSKQFTSSTSYNRGDST
HEMO-pp1	TPLPPTSAHGNVAEGETKPD
HEP2-pp1	GSKGPLDQLEKGGETAQSAD
IGHG1-pp1	EALHNHYTQKSLSLSPG
IGHG1-pp2	ALHNHYTQKSLSLSPG
IGKC-pp1	NALQSGNSQESVTEQD
IGKC-pp2	NALQSGNSQESVTEQDSKD
IGLC3-pp1	SSPVKAGVETTTPSKQ
ITIH4-pp1	NVHSGSTF
K1C9-pp1	SRSGGGGGGGLGSGGSIRSSY
KV105-pp1	DIQMTQSPSTLSASVGD
KV116-pp1	DIQMTQSPSSLSASVGD
THRB-pp1	QVTVAMTPR
THRB-pp2	GLDEDSDRAIEGR
TRFE-pp1	VAFVKHQTVPQNTGGKNPD

Supplementary Figures

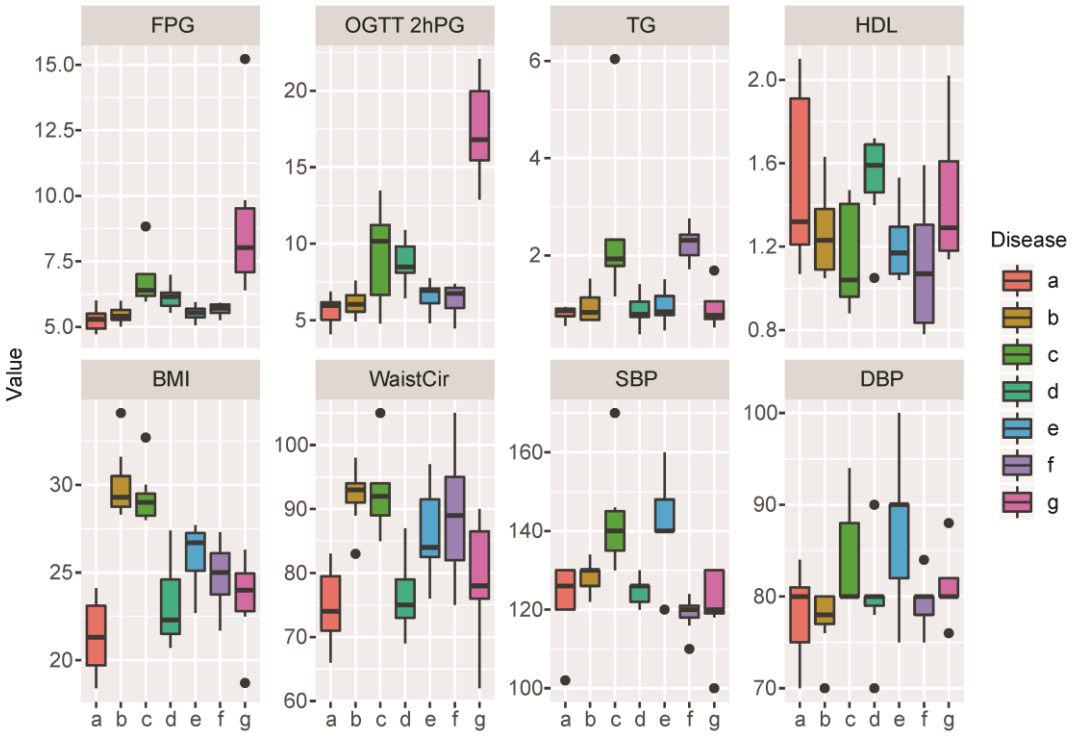

Figure S1 Boxplots of clinical differences between all collected seven groups of samples. The centers of the boxes represent the median values. The bottom and top boundaries of the boxes represent the 25th and 75th percentiles. The whiskers indicate 1.5 times of the interquartile range. The dots represent points falling outside this range. 2hPG: 2-hour postprandial plasma glucose; BMI: body mass index; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HDL: high density lipoprotein; OGTT: oral glucose tolerance test; SBP: systolic blood pressure; TG: triglyceride; WaistCir: waist circumference.

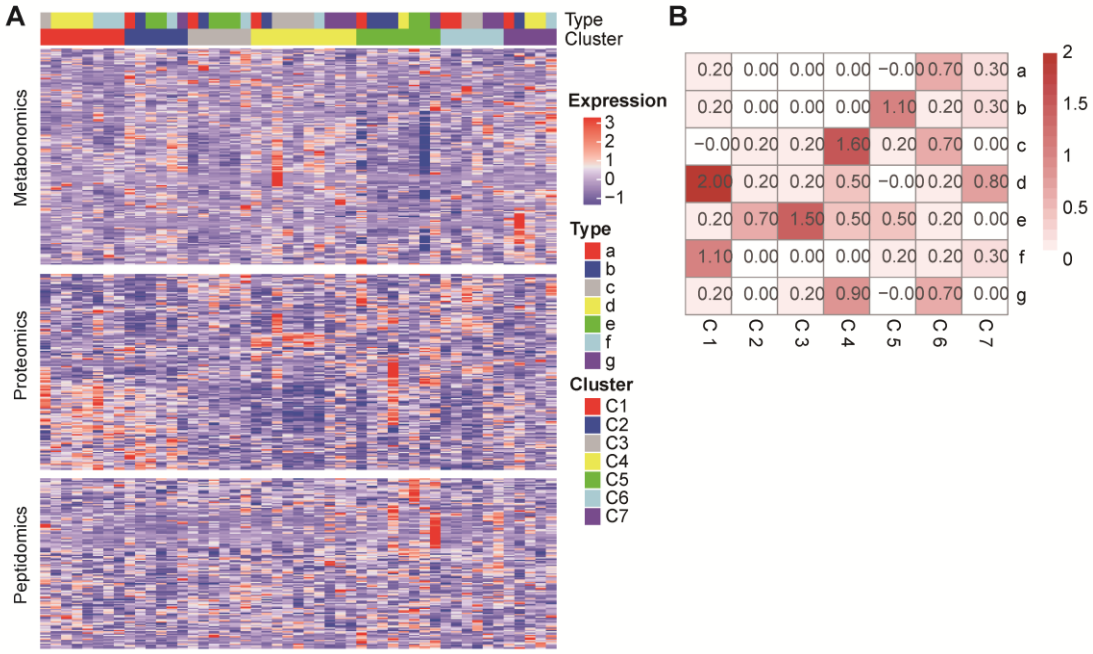

Figure S2 Clustering the samples based only on the omics data. **A** Clustering results. The central heatmap displays the standardized expression of metabolomics, proteomics and peptidomics. Each column corresponds to a patient and each row corresponds to a molecule. The top two rows indicate the original patient groups (a to g), the clustering results (C1 to C7). **B** Significance of the overlaps between the different clusters (represented by the columns) and the patient groups (represented by the rows) according to Fisher's exact test.

Supplementary methods

Metabolome profiling

Metabolomics and lipidomics profiling was performed with a Waters UPLC system coupled with a Q Exactive HF mass spectrometer (Thermo Fisher Scientific, Rockford, IL, U.S.A.) [64, 65]. The separation was performed with a 2.1×100 mm ACQUITY^{TM} 1.7 μm C8 column in ESI positive ion mode, and the mobile phase consisted of water with 0.1% formic acid (A) and acetonitrile (B). The gradient program was as follows: 5% B, held for 1 min, linearly changed to 100% B within 24 min, held for 4 min, then returned to 5% B, held 2 min. For the ESI negative ion mode, the separation was performed with a 2.1×100 mm ACQUITY^{TM} 1.8 μm T3 column, and the mobile phase consisted of 6.5 mM ammonium bicarbonate water solution (C) and 6.5 mM ammonium bicarbonate in 95% methanol and water (D). The gradient program was as follows: 2% D, held for 1 min, linearly changed to 100% D over 18 min, held for 4 min, then returned to 2% D, held for 2 min. The flow rate was 0.35 mL/min, and the column temperature was kept at 50 ℃ in positive ion mode and 55 ℃ in negative ion mode.

The separation of the lipid metabolites was performed with a Waters UPLC C8 ACQUITY column (2.1 mm × 100 mm × 1.7 μm) (Milford, MA, USA). The elution solvent consisted of A (ACN:H2O = 60:40, v/v) and B (IPA:ACN = 90:10, v/v), both of which contained 10 mM ammonium acetate. The elution program started at 32% B for the initial 1.5 min, followed by a linear increase to 85% B over the next 14 min. Over 0.1 min, solvent B was rapidly increased to 97% and then maintained for 2.4 min for a column flush. Subsequently, the elution solvent was returned to 32% B within 0.1 min and maintained for 2 min for column equilibration. The column temperature was set to 55 ℃, and the flow rate was 0.26 ml/min. The spray voltage was 3.5 kV for positive mode and 3.0 kV for negative mode. The capillary temperature was maintained at 300 ℃. The auxiliary gas heater temperature was 350 ℃. The flow rates of the sheath gas and the auxiliary gas were 45 arb and 10 arb, respectively. The S-lens RF level was 50. The AGC target was set to a 3106 ion capacity, and the maximum IT was 200 ms. The mass resolution was set to 120,000 and 30,000 for full scan MS and data-dependent MS/MS, respectively.

GC-MS analysis was also performed for the metabolic profiling. A QP 2010 GC-MS system (Shimadzu, Japan) with a DB-5 MS fused silica capillary column (30 m × 0.25 mm × 0.25 μm, Agilent Technologies, USA) was used. A pseudotargeted GC-MS metabolomics method was used as previously reported [66].

Quality control (QC) samples were prepared by mixing equal aliquots of serum from each real sample, and QC samples were run (one QC after each 8 serum samples). The reproducibility of the metabolite ions was also evaluated with relative standard deviation (RSD%) in the QC samples. In this study, 78.3% of ions had RSD% less than 20%, and 91.1% of ions had RSD% less than 30%.

Proteome profiling

One microliter of serum was diluted with 100 μL 25 mM ammonia bicarbonate (ABC, pH 8.5), and the protein concentration was determined by a BCA assay (Beyotime, China). The proteins were reduced in 20 mM dithiothreitol (DTT, Merck, Germany) at 95 ℃ for 5 min, and the products were alkylated in 40 mM iodoacetamide (IAA, Merck, Germany) at room temperature in the dark for 30 min. Next, 2 μg of trypsin (Promega, WI) was added and incubated at 37 ℃ for 16 h.

Each sample was analyzed in technical triplicate with a nano-RPLC-MS/MS on a Q-Exactive MS (Thermo, CA) coupled with an Easynano LC system (Thermo, CA). The mobile phases were buffer A (2% acetonitrile, 98% water, and 0.1% formic acid) and B (98% acetonitrile, 2% water, and 0.1% formic acid). Fused silica capillaries were purchased from Sino Sumtech (Handan, China). A C18 trap column (150 μm i.d. × 5 cm) was connected to a capillary separation column (75 μm i.d. × 15 cm). Both the trap and separation columns were made in-house and packed with Daiso C18 particles (5 μm, 100 Å, Osaka, Japan). A 110 min gradient was established, comprising 60 min of 6%−22% buffer B, followed by 30 min of 22%−35% buffer B, 10 min of 35%−80% buffer B and 10 min of 80% buffer B. The spray voltage was 2.5 kV, and the temperature of the ion transfer capillary was set to 275 ℃. The Q Exactive MS was operated in positive ion mode, and the 10 most intense ions were subjected to HCD fragmentation with a normalized collision energy of 28%. The MS scans were performed at a resolution of 70 000 from m/z 300 to 1800 (automatic gain control (AGC) value, 1E6; maximum injection time, 100 ms), and the data were acquired in profile mode. The MS/MS scans were performed at a resolution of 17 500 (AGC, 1E5; maximum injection time, 60 ms), and the data were acquired in centroid mode using a 20 s exclusion window. The unassigned ions or those with a charge of +1 and >+7 were rejected. Then, the raw data were uploaded into Maxquant (v.1.6.1.0) and searched against the UniProtKB human complete proteome sequence database (release 2017_06, 24,148 entries). The search included cysteine carbamidomethylation as the fixed modification and methionine oxidation and acetylation of protein N-terminal as variable modifications. The searching tolerance for precursor ions was 10 ppm, and that for fragment ions was 20 ppm. Matching between runs with retention time window of 0.7 min and the label free quantification algorithm were performed. During proteome profiling, each individual sample was measured three times, and the average profiling result was adopted as the final one. The samples were profiled in two batches, and batch effects were removed with the R package sva [67].

Peptidome profiling

A total of 50 μL of serum supernatant was diluted with 250 μL of deionized water and denatured by boiling for 5 min. Then, the mixture was transferred to a centrifugal ultrafiltration tube and centrifuged (Eppendorf Centrifuge 5804 R) at 6000 g for 40 min. After washing twice with deionized water and 20% acetonitrile solution (v/v) containing 0.1% formic acid (v/v), all of the filtrate was collected, freeze-dried and redissolved in 50 μL of 0.1% formic acid solution (v/v). Twenty-five microliters of each diluted filtrate was mixed together to generate each QC sample. The remaining individual sample and QC sample were used for light and heavy labeling via a stable isotope dimethyl labeling method [68].

The peptide analysis was performed with nano-RPLC-ESI-MS/MS on an LTQ-Orbitrap Elite mass spectrometer coupled with a Dionex UltiMate 3000 RSLC-nano System (Thermo, San Jose, CA). The samples were loaded onto a 3 cm C18 trap column (200 μm i.d.) at a flow rate of 3 μL/min and separated on a 15 cm C18 column (150 μm i.d.) at a flow rate of 500 nL/min. The mobile phases A (100% water and 0.1% formic acid) and B (80% acetonitrile, 20% water, and 0.1% formic acid) were used with a 105 min gradient: 2% B for 10 min, 2–5% B for 3 min, 5–28% B for 60 min, 28–45% B for 15 min, 45–95% B for 1 min and 95% B for 5 min. The LTQ-Orbitrap Elite mass spectrometer was operated in a positive, data-dependent MS/MS acquisition mode. The ion transfer capillary temperature was 275 ℃, and the spray voltage was 2.7 kV. A full mass scan was acquired with the Orbitrap mass

analyzer from m/z 350 to 1650 at a resolution of 120000, and the top 20 parent ions with charge states ≥ 2 in the full scan were fragmented by collision-induced dissociation (CID) with 35% normalized collision energy. The dynamic exclusion function parameters were as follows: repeat count 1, repeat duration 30 s, and exclusion duration 90 s. The acquired raw MS/MS spectra from each sample were searched against the International Protein Index (IPI) human database with the UniProt website using Mascot Version 2.4.1 (Matrix Science). MaxQuant software (version 1.6) was used to perform the quantitative analysis. The search parameters for both searching modes were as follows: no specific proteolytic enzyme was specified; the oxidation of methionine (M) was the variable modification; the false discovery rate (FDR) cutoff was 0.01. Additionally, the precursor-ion mass error tolerance was 20 ppm, and the fragment-ion mass error tolerance was 0.8 Da for the Mascot search. Duplicates with dimethyl Lys 0 and N-term 0 as the light labels and dimethyl Lys 6 and N-term 6 as the heavy labels were selected for the Maxquant search.

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