ADIPOCYTE FATTY ACID-BINDING PROTEIN:
A PREDICTIVE MARKER OF METABOLIC SYNDROME

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Background

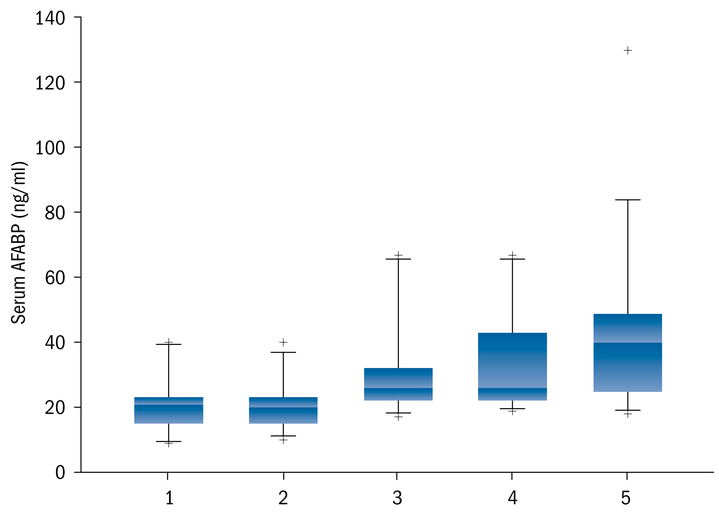
Adipocyte fatty acid–binding protein (A-FABP; also known as FABP-4) is a major cytoplasmic protein abundantly expressed in mature adipocytes and activated macrophages. A-FABP binds fatty acids with high affinity and functions in intracellular fatty acid trafficking, regulation of lipid metabolism, and modulation of gene expression. Emerging evidence suggests that A-FABP is closely associated with obesity, diabetes and metabolic syndrome.

We have previously demonstrated that circulating A-FABP concentrations are significantly higher in overweight/obese than in lean individuals. Age- and sex-adjusted serum A-FABP concentrations correlate positively with waist circumference, blood pressure, dyslipidemia and fasting insulin.

Pending patent EP1904082B1: METHOD FOR DETERMINING THE CONCENTRATION OF THE ADIPOCYTIC FORM OF THE FATTY ACID BINDING PROTEIN (A-FABP, FABP4, aP2)
Th invention relates to a method for determining the concentration of A-FABP protein for diagnostic and research of the metabolic syndrome, of non-insulin dependent diabetes, insulin resistance, obesity and related disorders.

Clinical study A

The study enrolled 486 individuals, of which 100 were healthy individuals, 100 patients with dyslipidemia without another criteria of metabolic syndrome, 86 patients with diabetes mellitus, type 2, 100 obese individuals, and 100 patients with metabolic syndrome.



1 = Healthy Controls, 2 = Dyslipidemia, 3 = Diabetes Mellitus - type 2, 4 = Obesity, 5 = Metabolic Syndrome

Clinical study B

Among 376 Chinese subjects who did not have the metabolic syndrome at baseline, 50 had developed metabolic syndrome at 5-year follow-up, and A-FABP was the only INDEPENDENT PREDICTOR OF DEVELOPMENT OF METABOLIC SYNDROME during the study. A-FABP was predictive of metabolic syndrome even after adjustment for each of its individual components. Thus, circulating A-FABP predicts development of metabolic syndrom independently of adiposity and insulin resistance. The baseline A-FABP concentration was significantly higher in subjects who had progressed to the metabolic syndrom at year 5: 19.9 ng/mL (interquartile range, 16.7 to 26.2 ng/mL) versus 15.0 ng/mL (interquartile range, 10.3 to 22.2 ng/mL) in subjects without the metabolic syndrom (sex-adjusted P=0.0002).

	1 (Men, <12.5 µg/L; Women, <16.4 µg/L)	2 (Men, 12.5–19.9 µg/L; Women, 16.4–25.6 µg/L)	3 (Men, >19.9 µg/L; Women, >25.6 µg/L)	P
Age, y	50.8±11.8	55.7±10.6	60.4±11.8	<0.001
BMI, kg/m^2	22.9±3.1	25.1±3.2	26.6±4.0	<0.001
WC, cm	75.5±7.9	81.5±8.5	85.1±11.0	<0.001
HT, yes/no	41/124	92/73	92/73	<0.001
FG, mmol/L	5.1±0.6	5.3±0.7	5.4±0.8	0,007
HDL, mmol/L†	1.5±0.4	1.3±0.3	1.3±0.4	<0.001
TG, mmol/L*†	0.9 (0.7–1.3)	1.10 (0.9–1.6)	1.5 (1.0–2.1)**	<0.001
LDL, mmol/L†	3.1±0.8	3.4±0.8	3.6±0.8	<0.001
HOMA-IR*	1.5 (1.1–2.1)	1.9 (1.3-2.7)	2.2 (1.4–3.3)	0,062
≥3 MetS components, %‡	8 (13/165)	31.1 (51/164)	42.9 (70/163)	<0.001
No MetS components, %‡	50.3 (83/165)	17.7 (29/164)	9.8 (16/163)	<0.001

WC indicates waist circumference; HT, hypertension; FG, fasting glucose; TG, triglycerides; and LDL, low-density lipoprotein. Data are mean ±SD or median (interquartile range) unless otherwise indicated.
** Log transformed before analysis; † Includes only subjects not on anti–lipid-lowering treatment; ‡ Excluded 3 patients on lipid-lowering drugs without available pretreatment lipid profile*

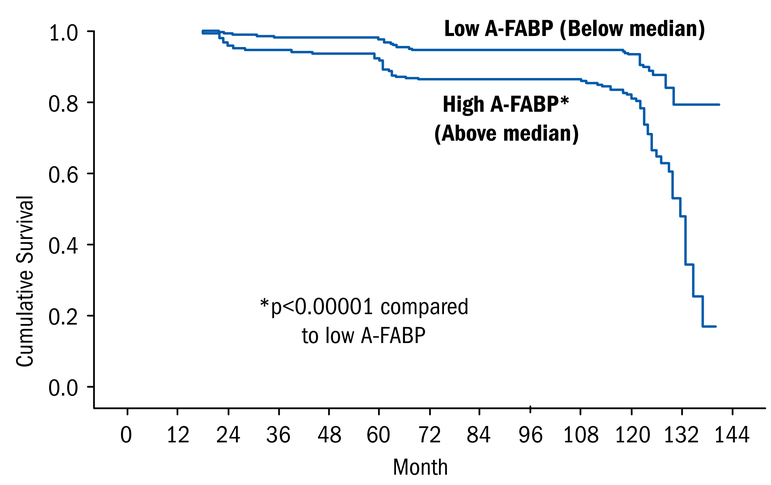
In multiple stepwise logistic regression analysis, baseline A-FABP (P=0.001) and HOMA-IR (P=0.001) were the only independent predictors for the development of the metabolic syndrom at year 5.

Parameters	OR	95% CI	P
HOMA-IR*	2,88	1.58–5.22	0,001
A-FABP tertile 2 vs 1†	4,39	1.79–10.79	0,001
A-FABP tertile 3 vs 1†	4,65	1.82–11.88	0,001
A-FABP tertile 3 vs 2‡	1,06	0.52–2.17	0,878

Variables included in the original model are BMI, HOMA-IR, and A-FABP in sex-specific tertiles. n=373.
** Log transformed before analysis; † Tertile 1 as reference with OR=1; ‡ Tertile 2 as reference with OR=1*

Clinical study C

In a 10-years follow-up study, the plasma A-FABP levels was found to be a STRONG PREDICTOR of type 2 diabetes independently of the traditional risk factors including obesity, insulin resistence, or glycemic index. Ref



Cumulative survival (by the Kaplan Meier method) for the development of DM over a median follow up of 10.0 years for subjects with A-FABP above and below sex-specific median.

Clinical study D

Degenerative aortic valve disease shares many features with atherosclerosis. The initial plaque of aortic stenosis is similar to that seen in coronary artery disease. A significant proportion of patients with severe aortic stenosis have no coronary atherosclerosis; therefore, the study was designed to survey the risk in such individuals, and enrolled two groups assessed by coronary angiography:

- group 1 (N= 64) - patients with AoS and without coronary artery disease (CAD)
- group 2 (N= 42) - control group; patients without AoS and CAD.

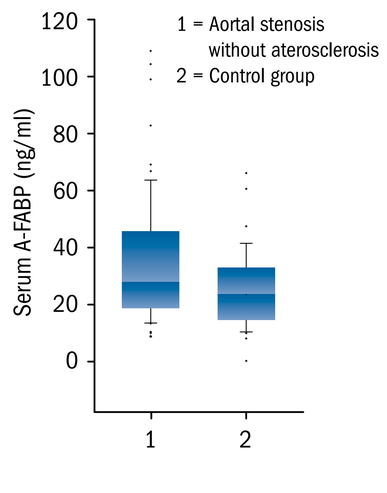
Baseline characteristics

Basic characteristics	AoS without CAD	Control group
Male gender (%)	56,5	53,9
Age (mean ± SD)	69.0 ± 9.8	62.9 ± 11.2
Hypertension (%)	62,9	61,5
Diabetes mellitus (%)	25,8	18
Cigarette smokers (%)	12,9	15,4
Hyperlipidemia (%)	37,1	51,3
Obesity (BMI ≥ 25) (%)	37,1	41
Chronic renal failure (%)	3,2	0
Periphery artery disease (%)	4,8	2,6
Atrial fibrilation (%)	6,5	7,7
Aspirin therapy (%)	33,9	43,6
Statin therapy (%)	25,8	33,3
ACE inhibitors (%)	40,3	38,5
NSAID therapy (%)	1,6	2,6
Severe aortic stenosis (%)	91,9	0
Moderate aortic stenosis (%)	8,1	0
NYHA class II	46,8	51,3
NYHA class III	40,3	15,4
NYHA class IV	8,1	0

Limitation of the study: clinical groups are not matched to age.

Group	N	Median	25%	75%
Aortal stenosis without aterosclerosis	64	27,9	18,4	45,3
Control group	42	19,9	14,4	32,74

Mann–Whitney–Wilcoxon test: P < 0.02



Conclusion from the study D:

- patients with aortal stenosis without atherosclerosis are under the strong risk of atherosclerosis development
- results support PROGNOSTIC value of A-FABP

Conclusion

Given the data mentioned above, the BioVendor Human Adipocyte FABP ELISA (IVD, CE-marked) is thought to be an efficient tool for prediction of diabetes mellitus, metabolic syndrome in relation to cardiovascular morbidity and mortality.

References:

1. Stejskal D, Karpisek M. *Adipocyte fatty acid binding protein in a Caucasian population: a new marker of metabolic syndrome?* Eur J Clin Invest. 2006 Sep;36(9):621-5.
2. Xu A, Tso AW, Cheung BM, Wang Y, Wat NM, Fong CH, Yeung DC, Janus ED, Sham PC, Lam KS. *Circulating adipocyte-fatty acid binding protein levels predict the development of the metabolic syndrome: a 5-year prospective study*. Circulation. 2007 Mar 27;115(12):1537-43.
3. Tso AW, Xu A, Sham PC, Wat NM, Wang Y, Fong CH, Cheung BM, Janus ED, Lam KS. *Serum adipocyte fatty acid binding protein as a new biomarker predicting the development of type 2 diabetes: a 10-year prospective study in a Chinese cohort*. Diabetes Care. 2007 Oct;30(10):2667-72.