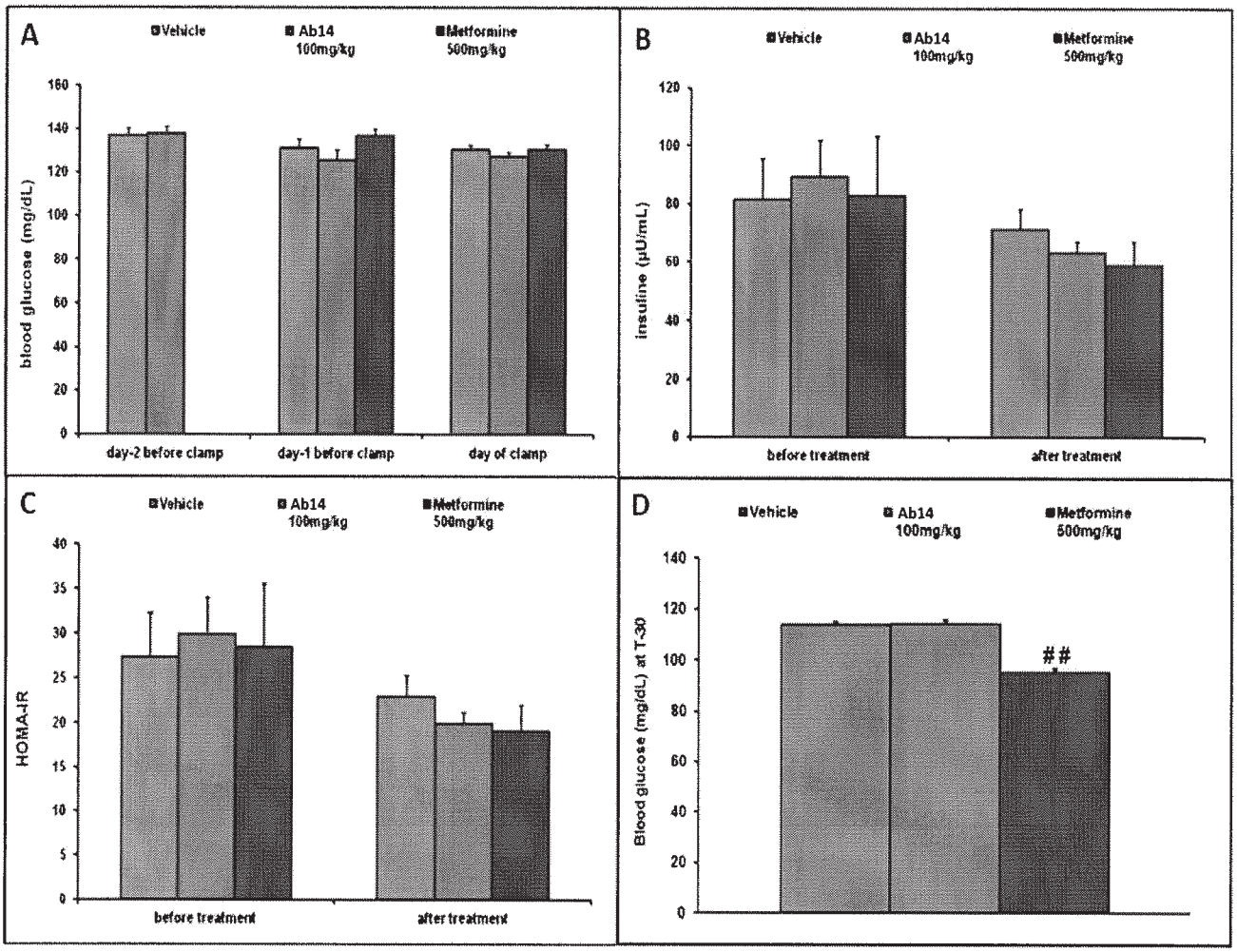


Figure 1: Blood glucose and plasma insulin levels before and after treatment.

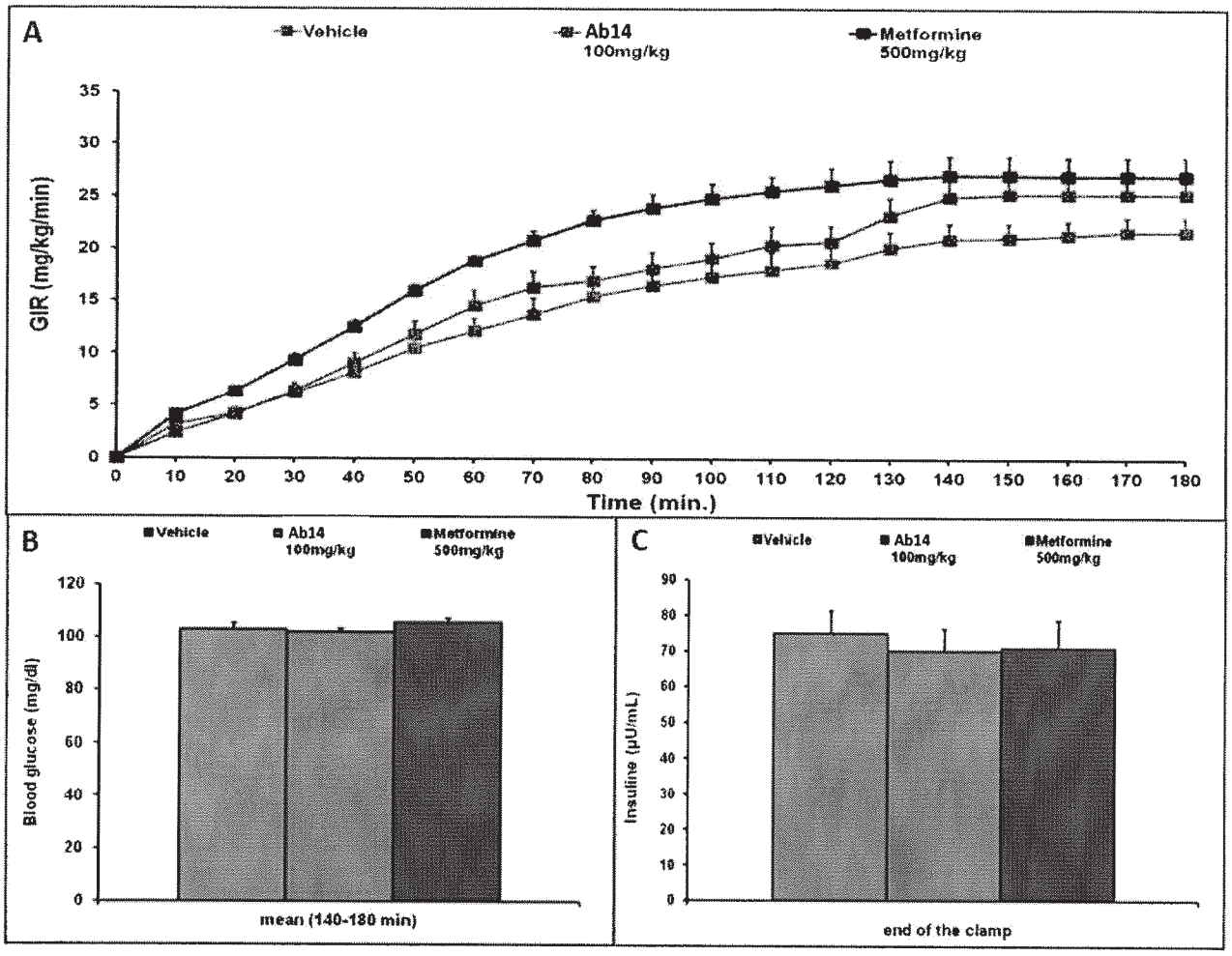


Figure 2: Glucose infusion rate evolution during clamp procedure.

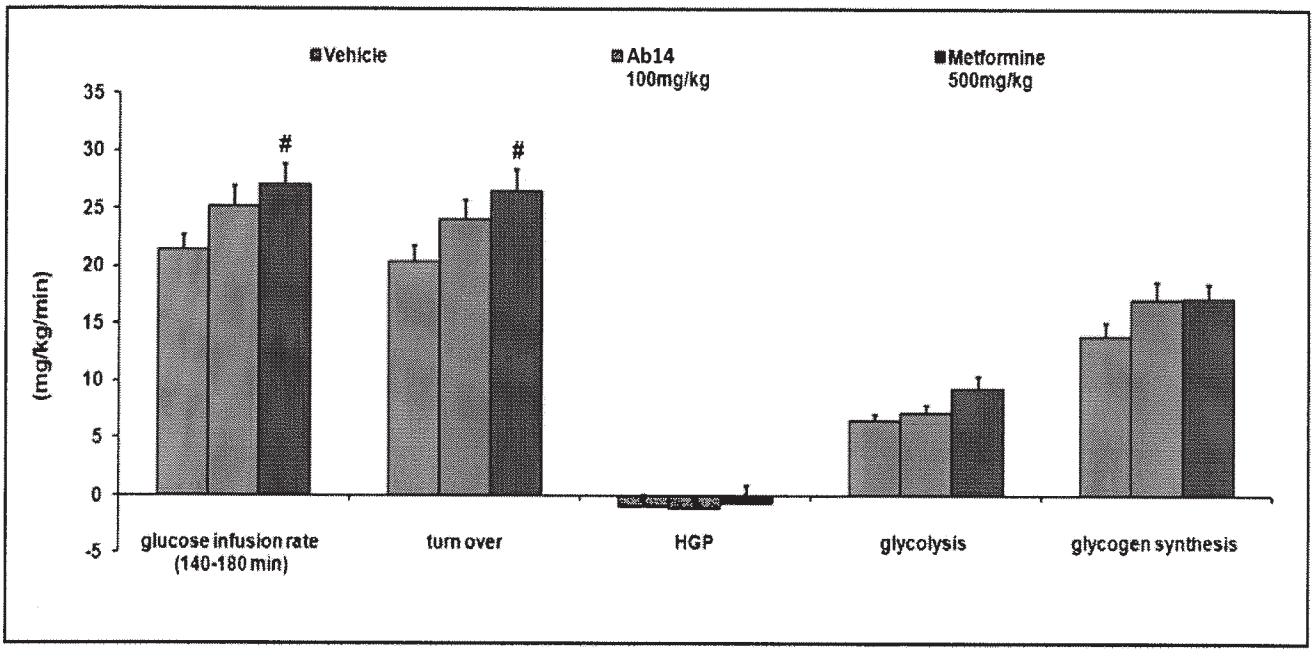


Figure 3: Measured glucose flux.

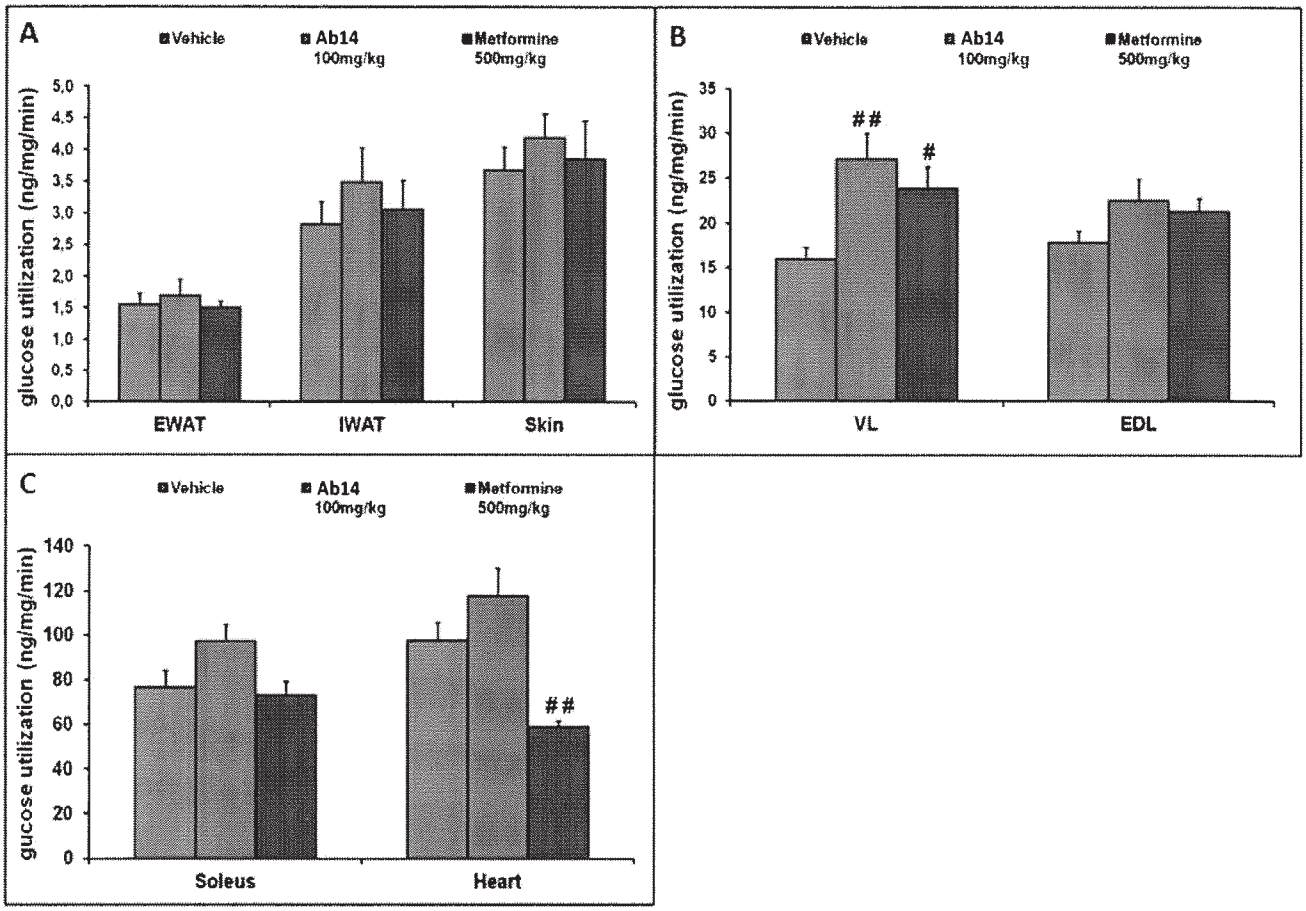


Figure 4: In vivo tissues specific glucose utilization.

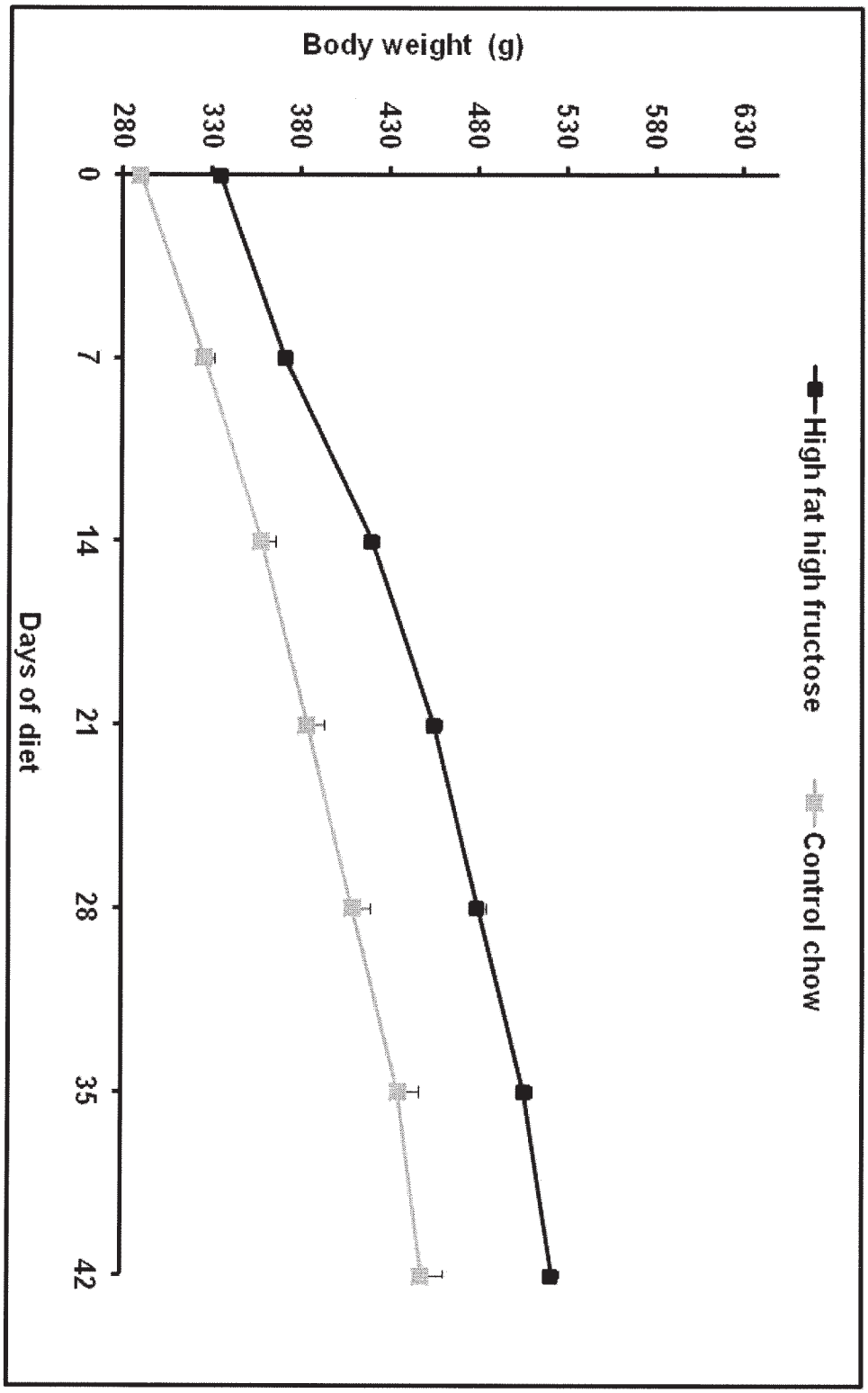


FIG. 5. Body weight follow-up during the diet

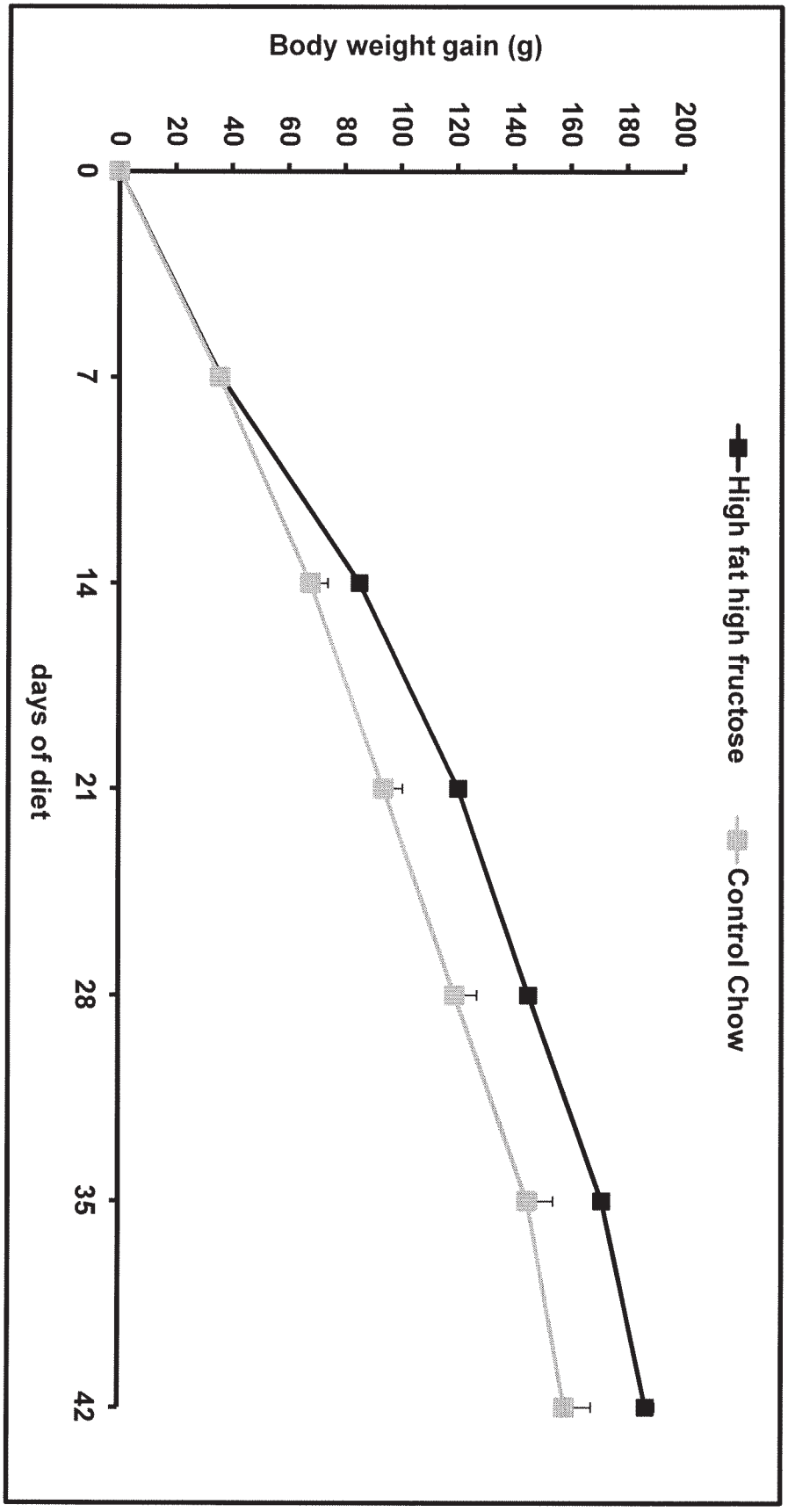


FIG. 6. Body weight gain follow-up during the diet period

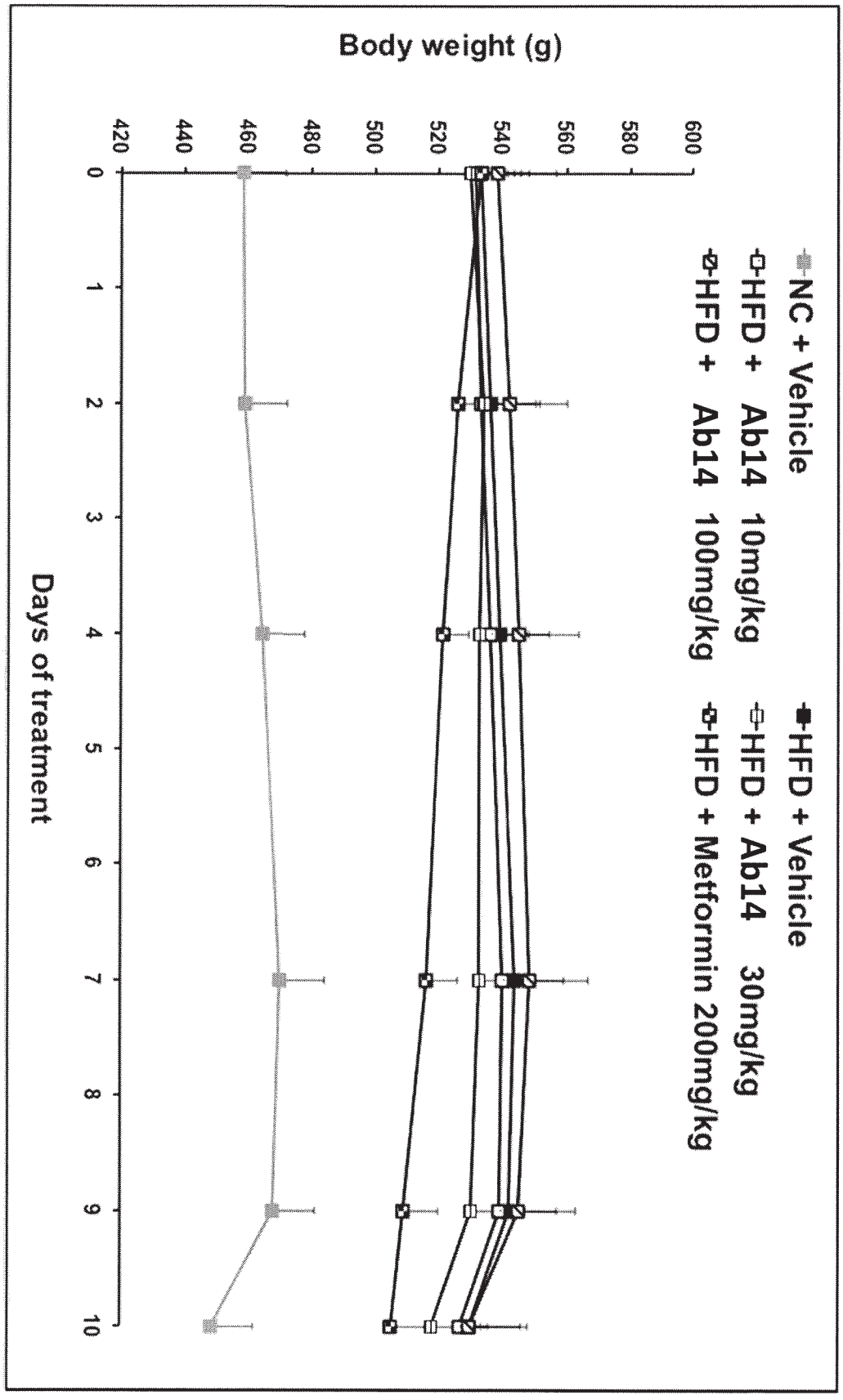


FIG. 7. Body weight follow-up

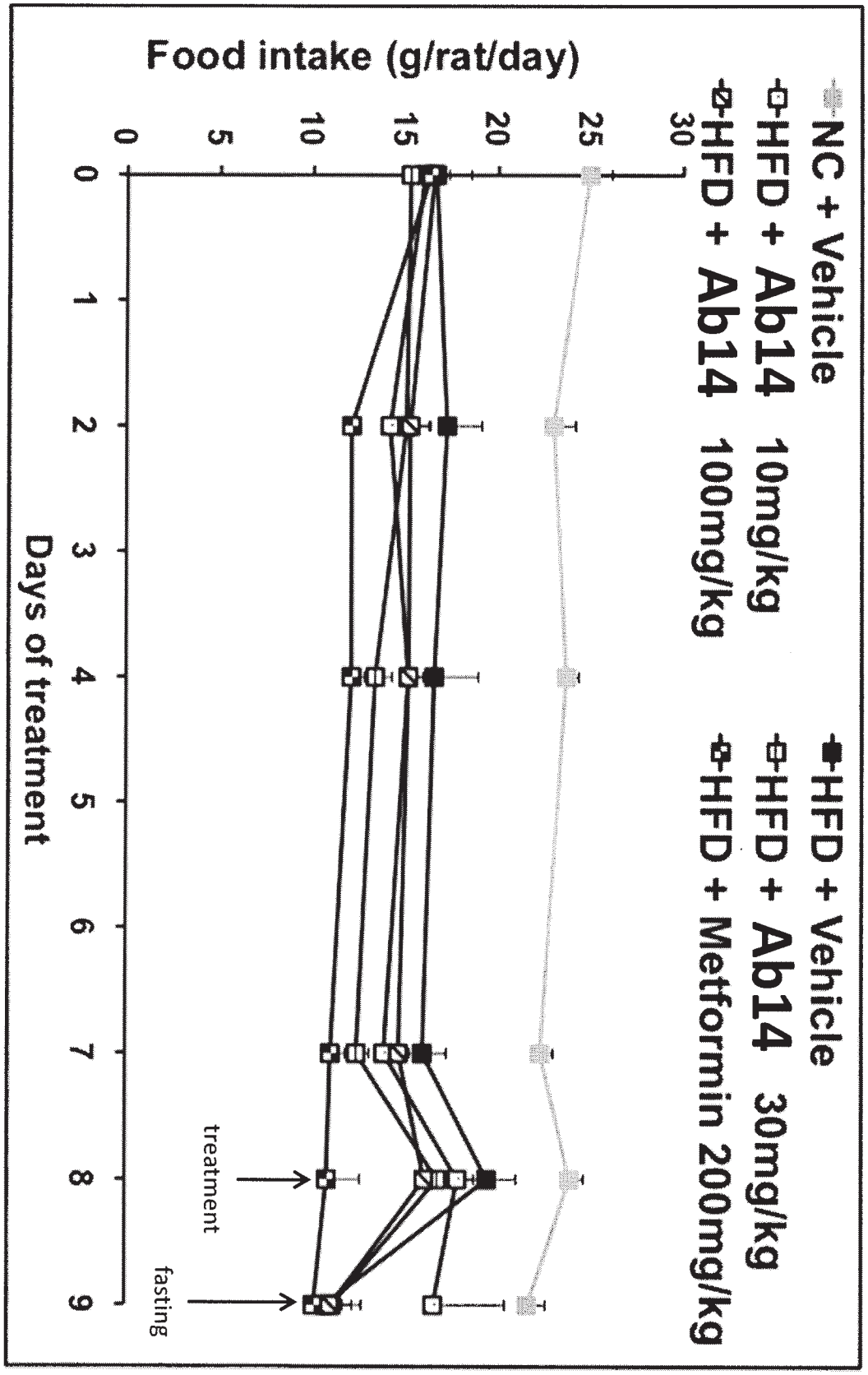
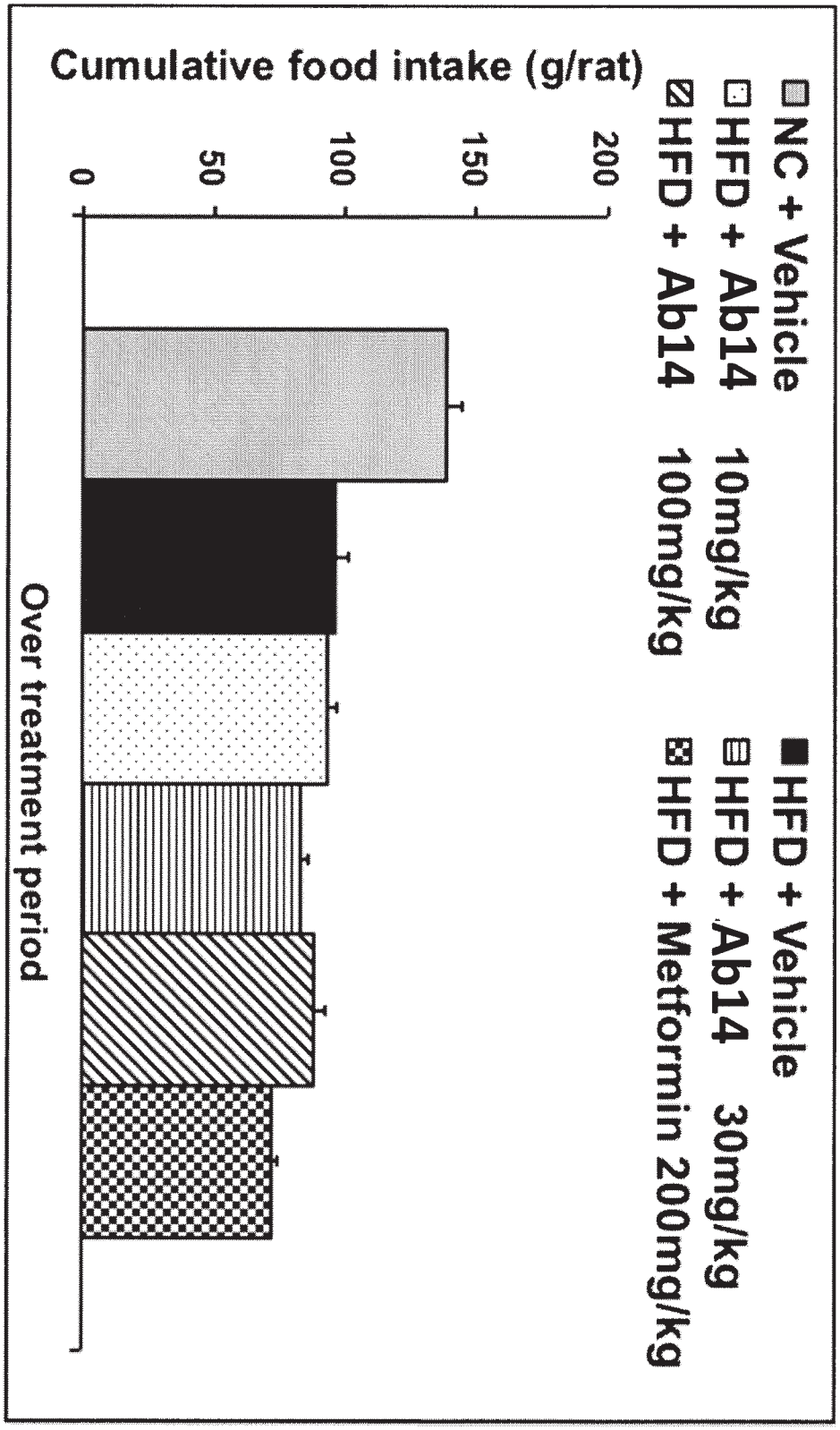


FIG. 8A. Food intake follow-up before surgery

FIG. 8B. Cumulative Food Intake



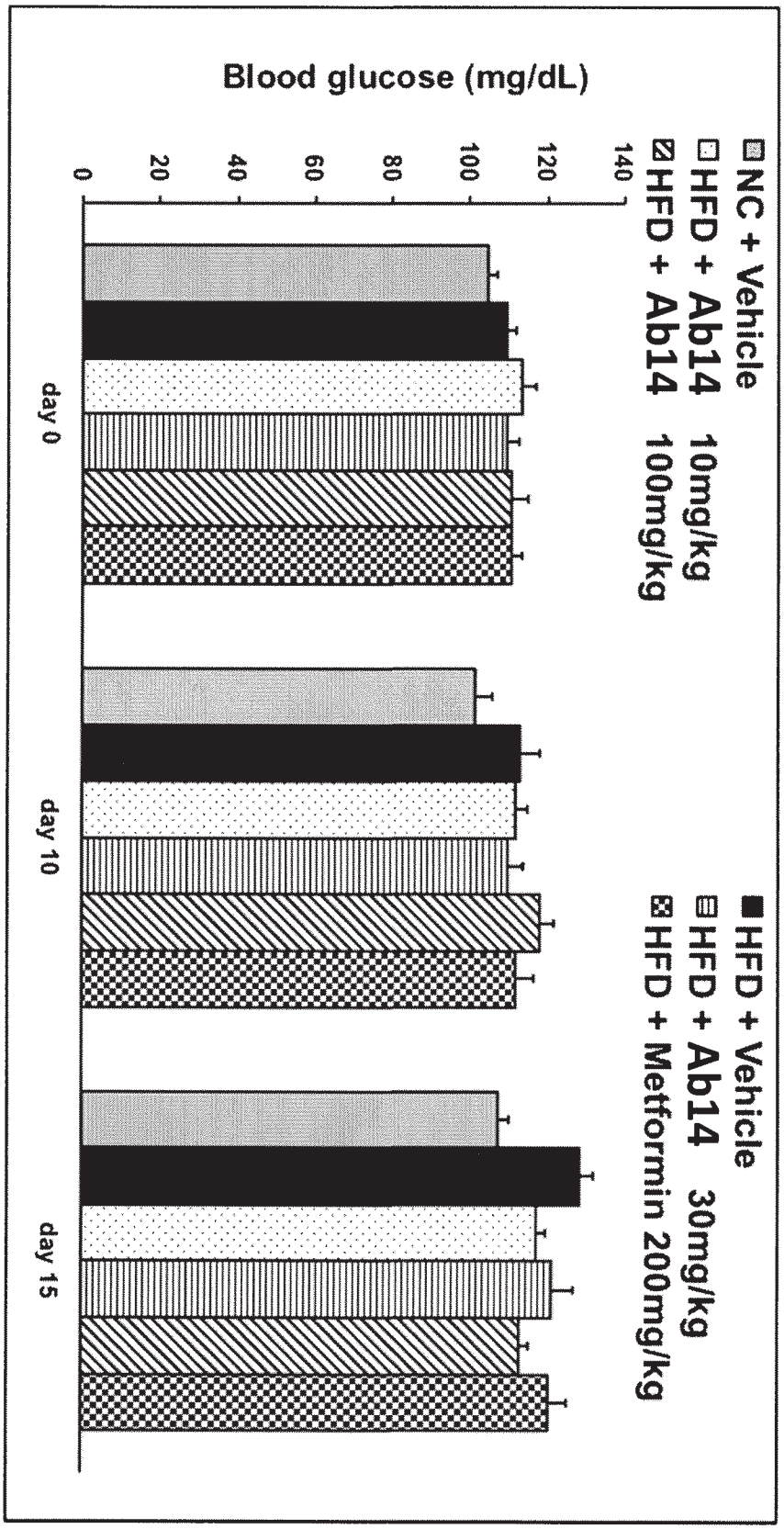


FIG. 9. Fasting Blood Glucose

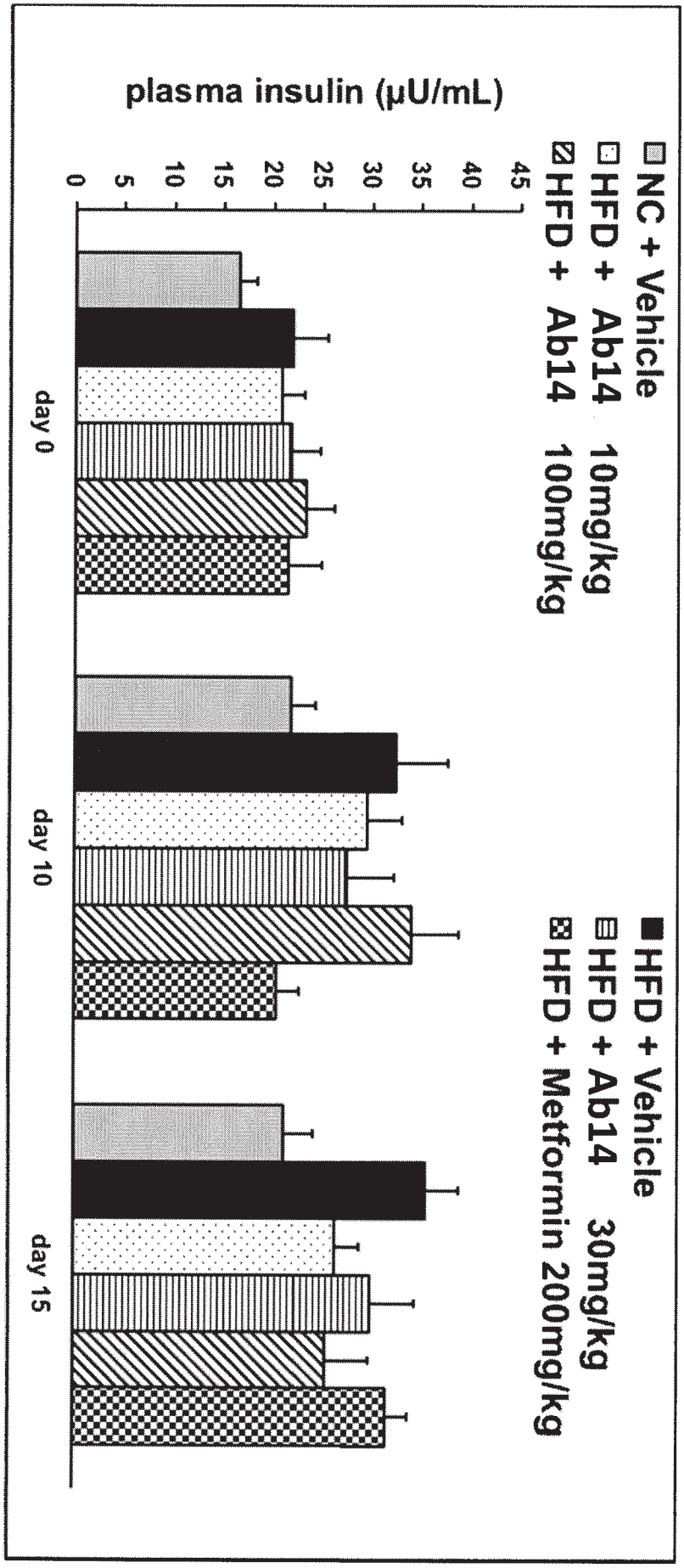


FIG. 10. Fasting Plasma Insulin

FIG. 11. Plasma insulin and C peptide during clamp procedure

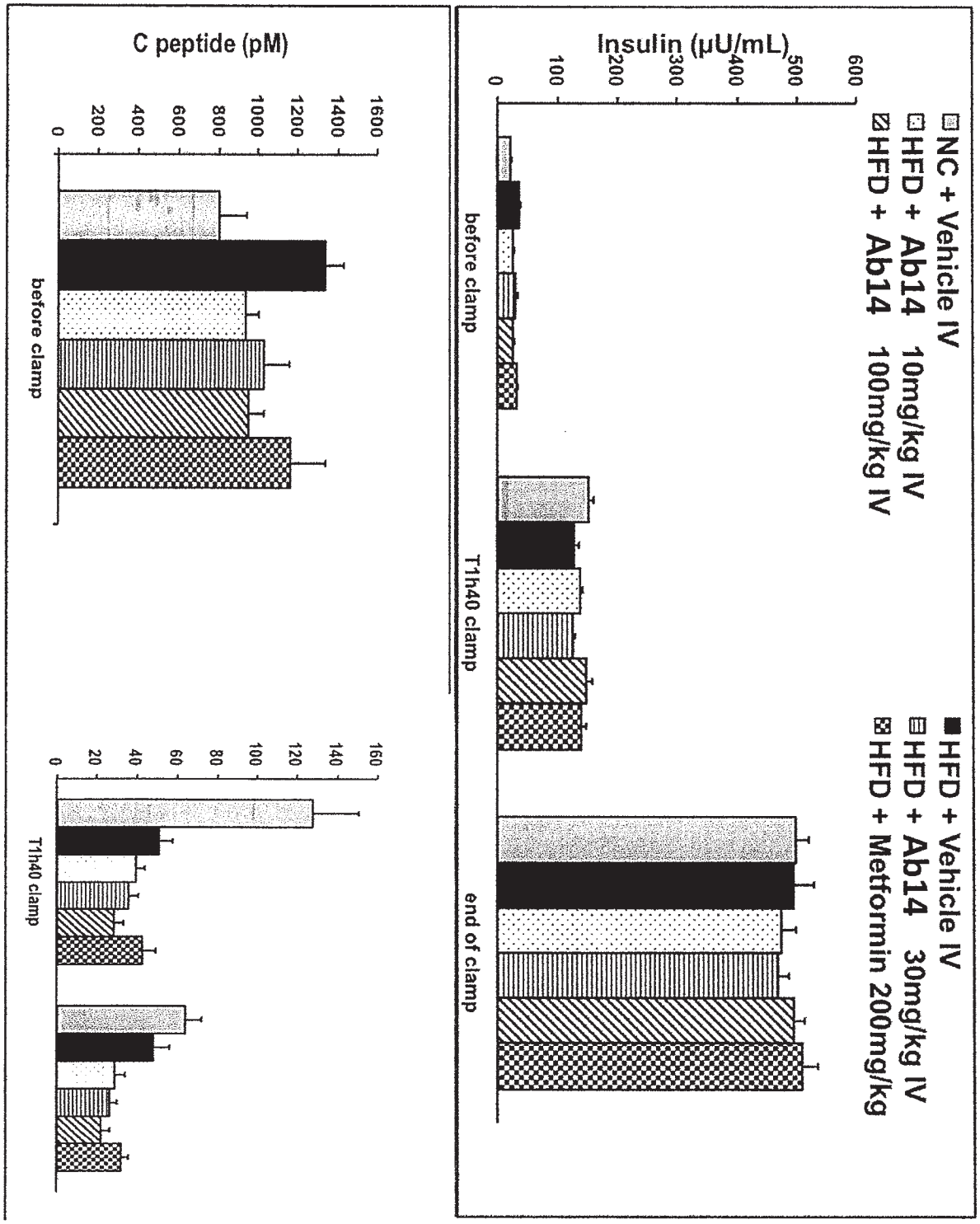


FIG. 12. HOMA-IR.

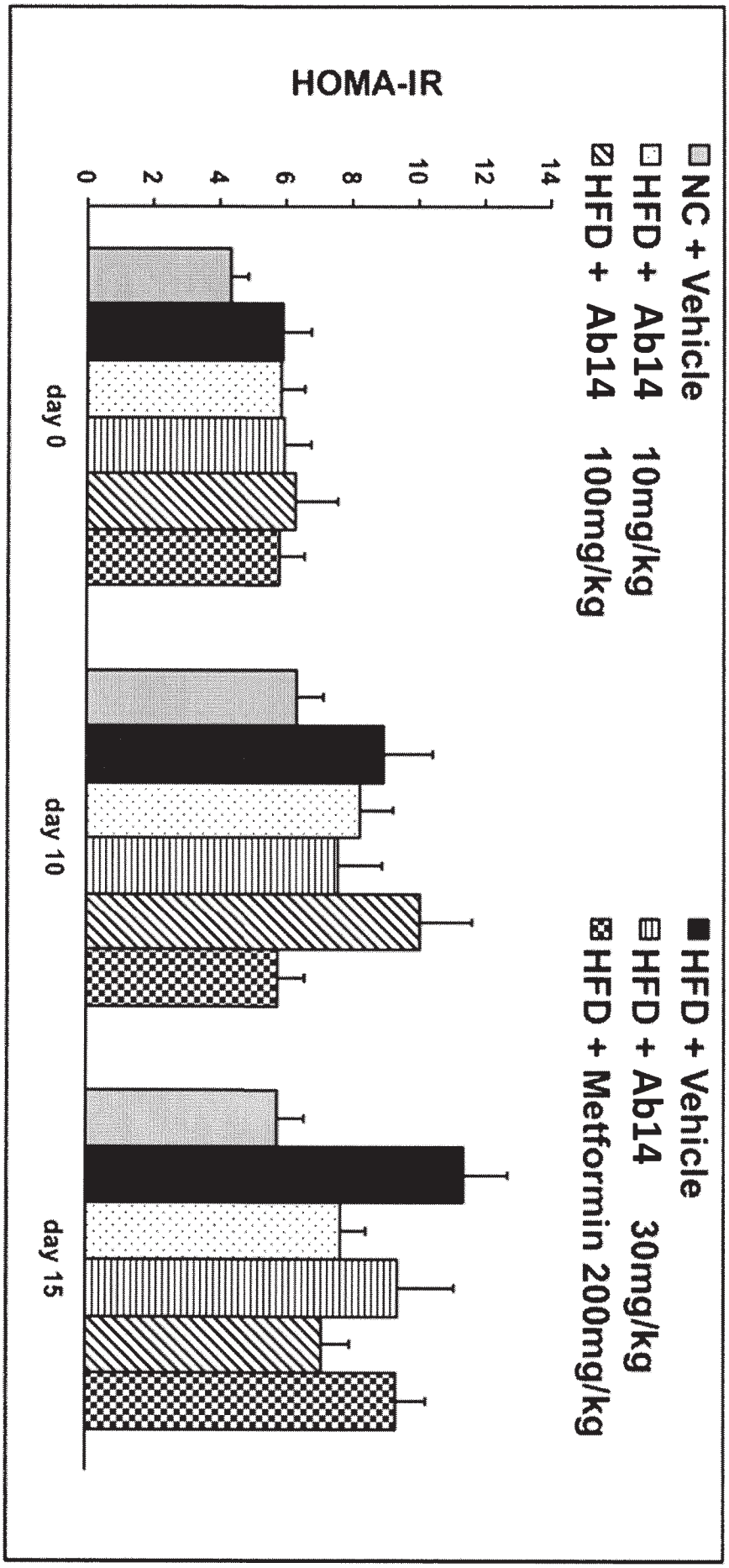


FIG. 13. Hyper-insulinemic clamp.

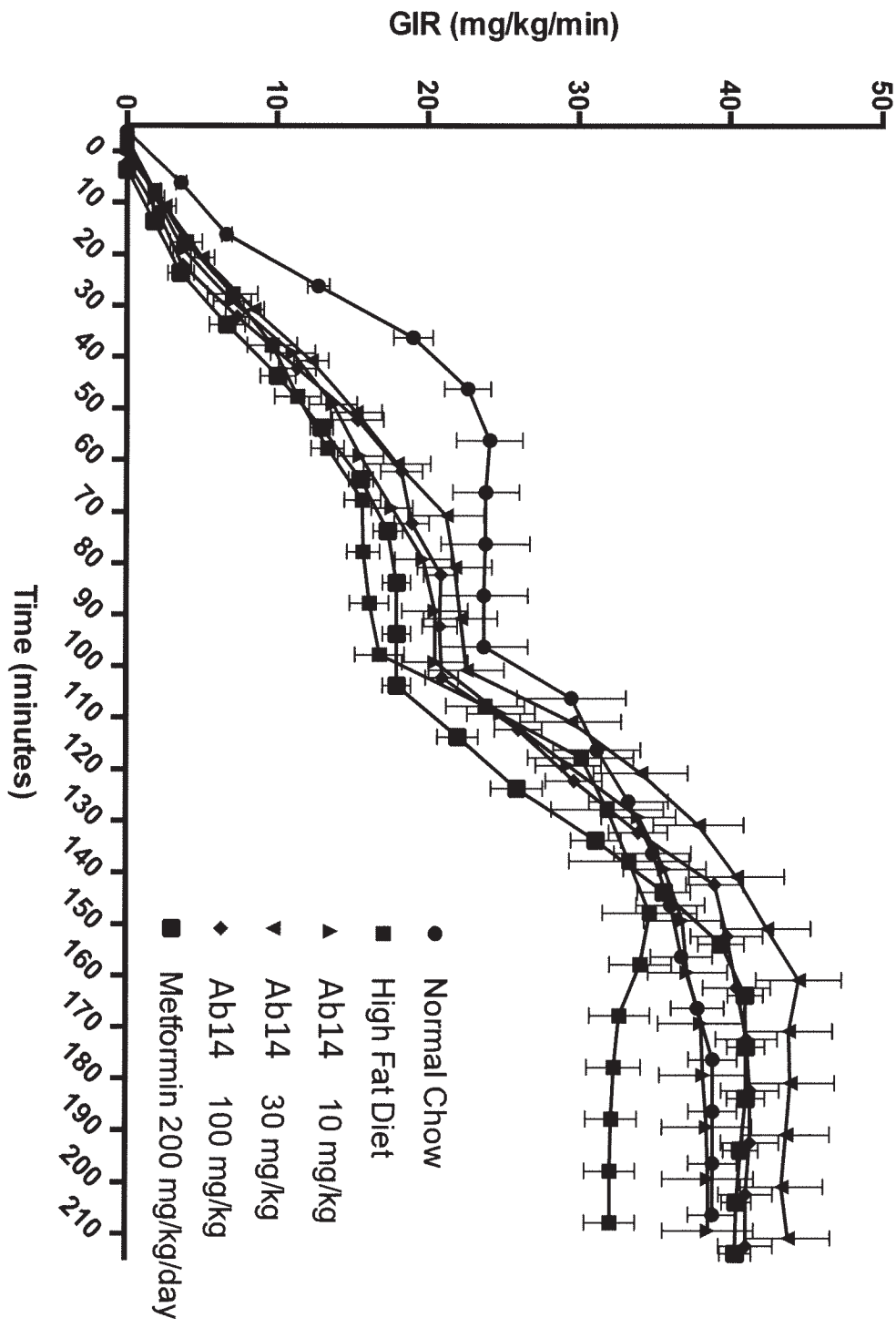
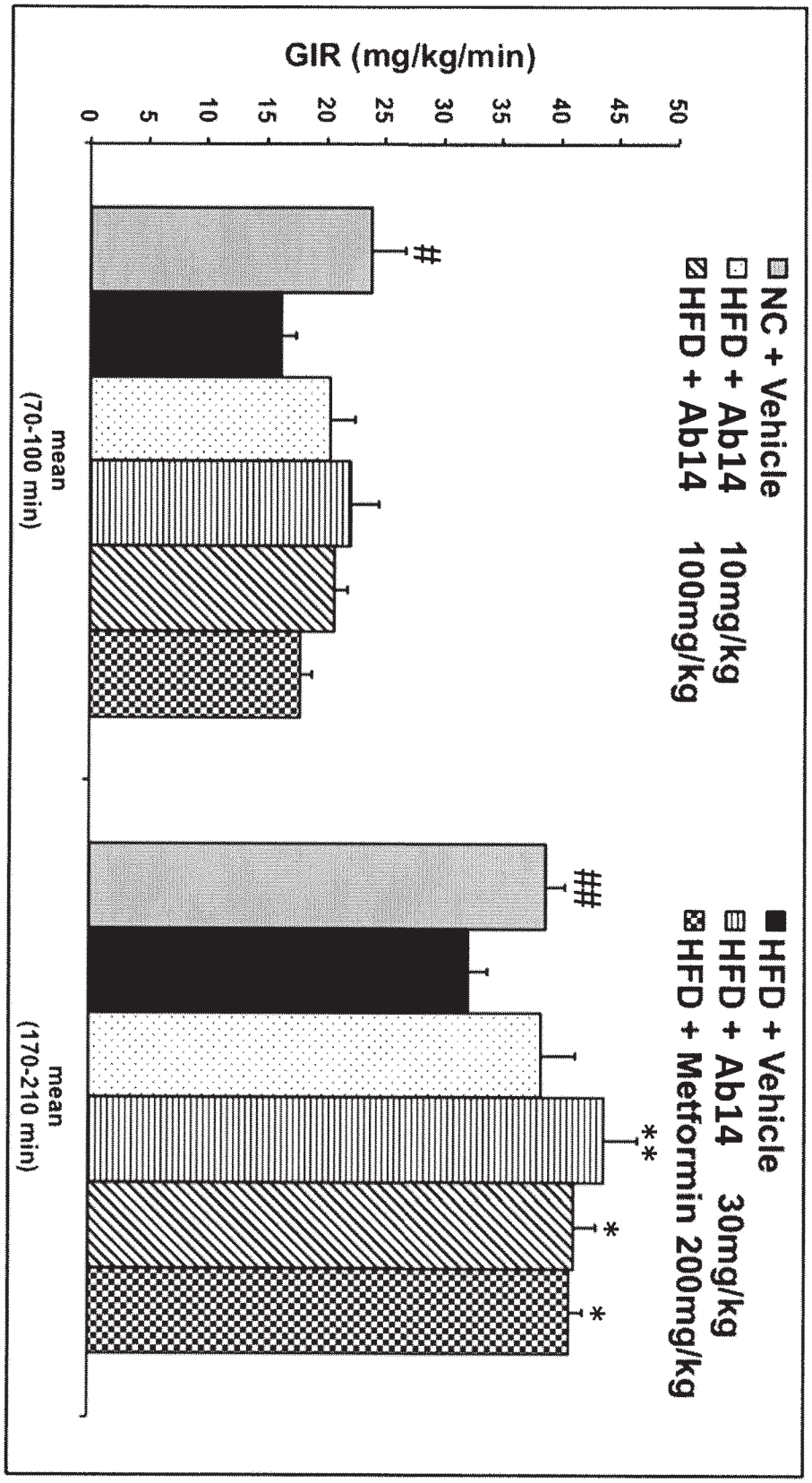


FIG. 14. Glucose infusion rate after two weeks of treatment



T-test (one-tail) vs HFD. #:p<0.05; ##:p<0.01
One way ANOVA + Dunnett' spost test vs HFD. *:p<0.05; **p<0.01

FIG. 15. Glucose fluxes after 15 days of treatment during clamp procedure with 5mU/kg/min insulin

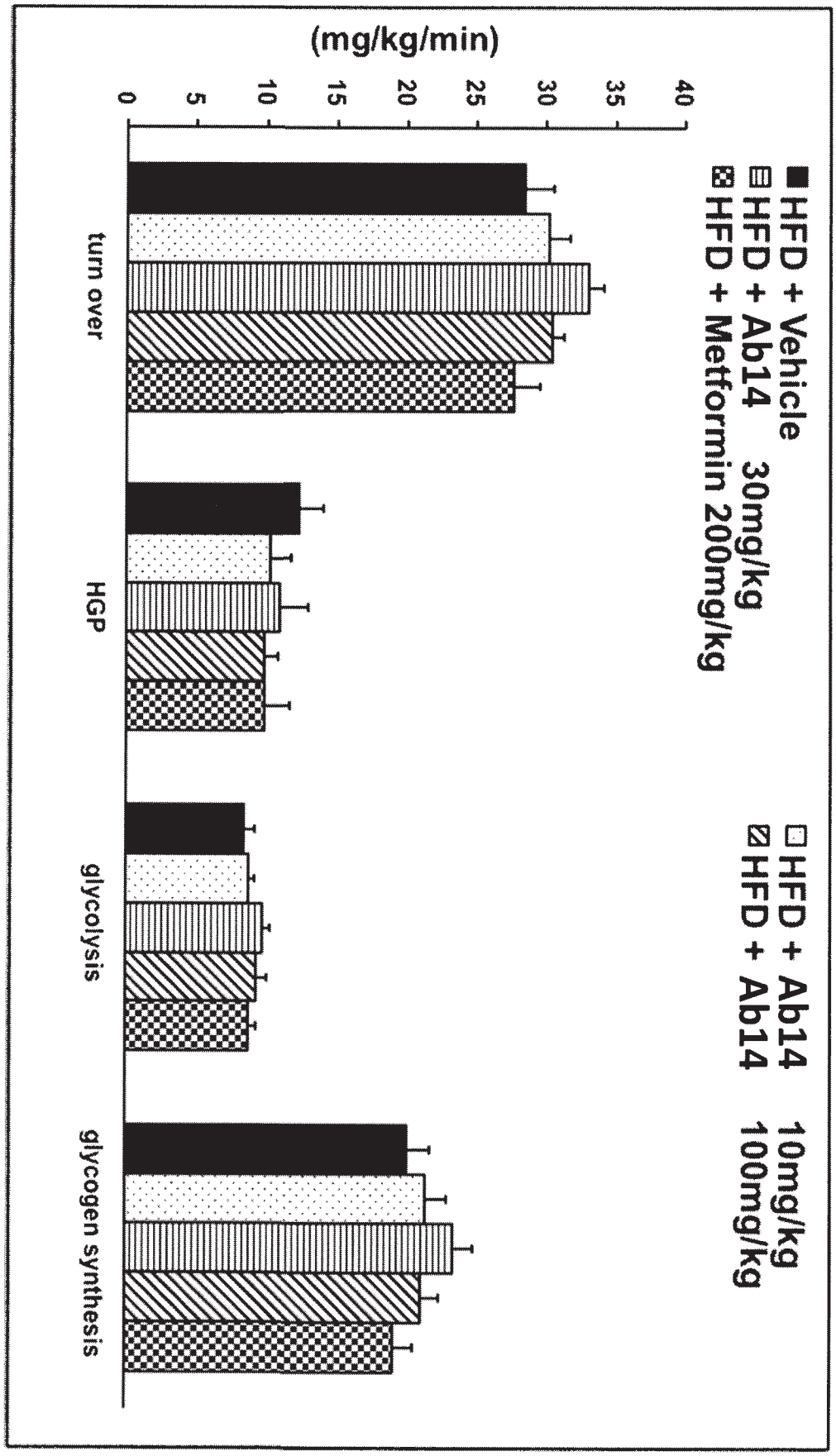
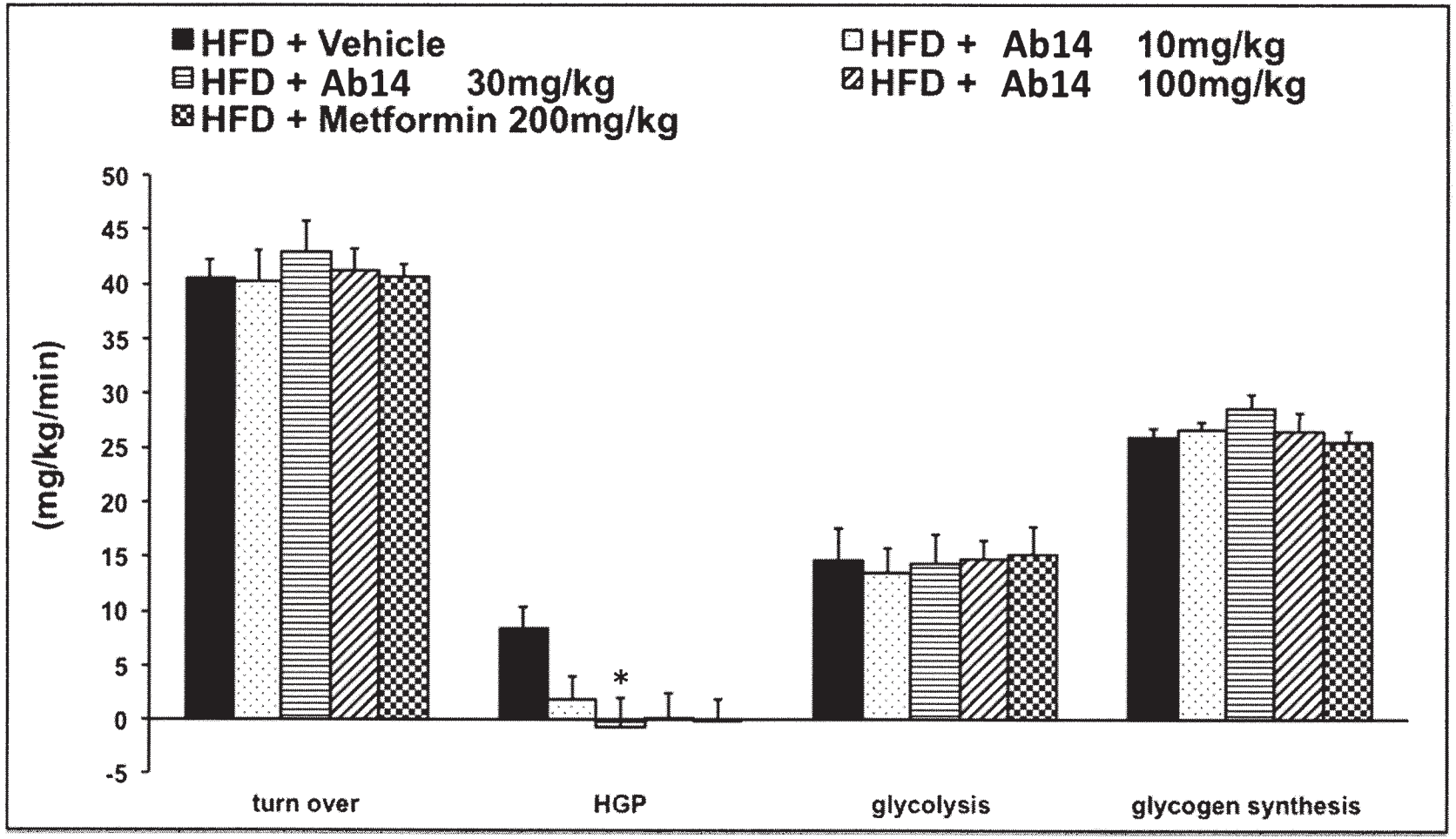


FIG. 16. Glucose fluxes after 15 days of treatment during clamp procedure with 15mU/kg/min insulin



One way ANOVA + Dunnett's post test vs HFD. *:p<0.05

FIG. 17. Mean toxicokinetic profiles of an anti-CGRP antibody (Ab6) following i.v. bolus injection into male Sprague-Dawley rats

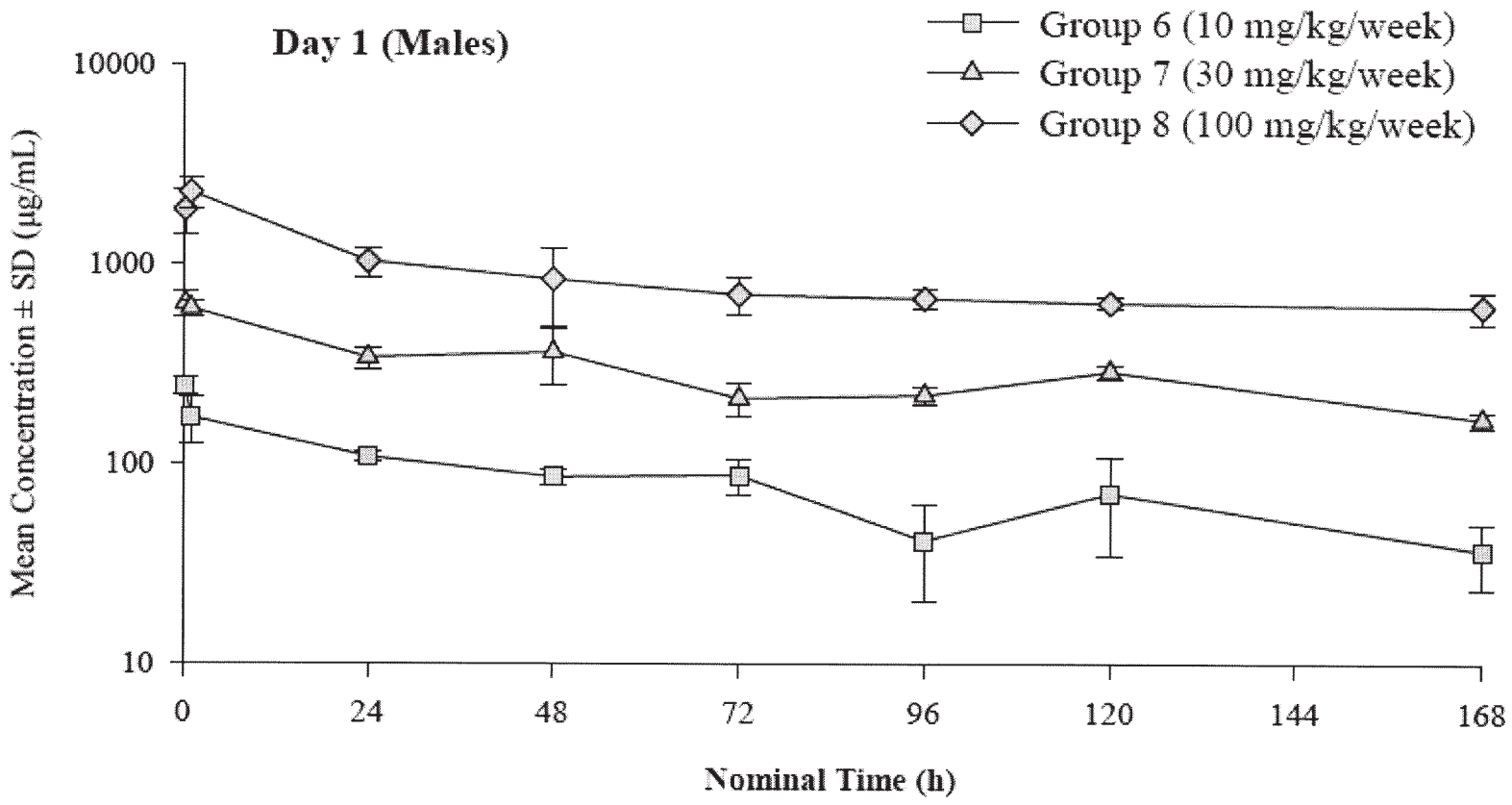


FIG. 18

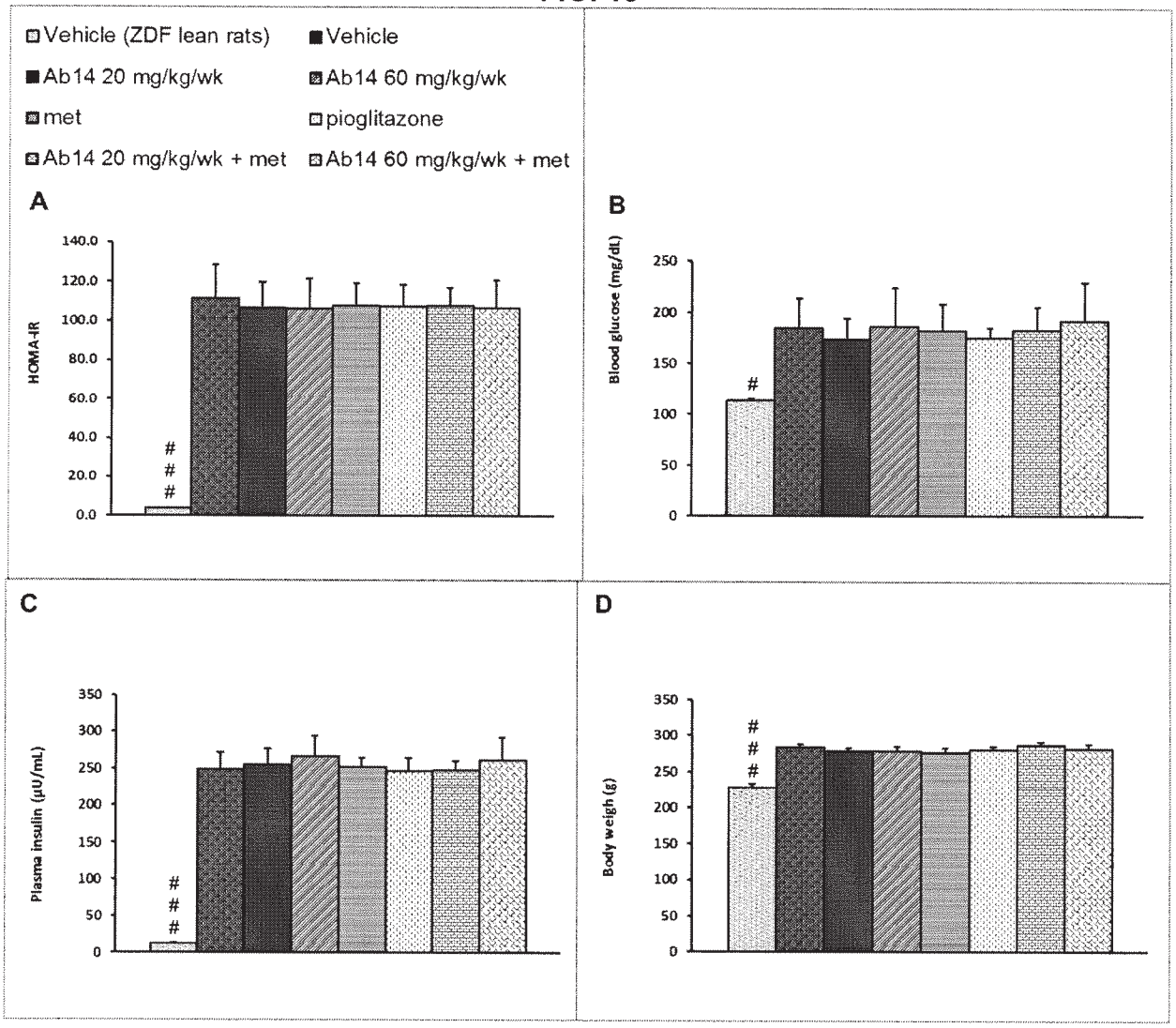

Vehicle (ZDF lean rats)
Vehicle
Ab14 20 mg/kg/wk
Ab14 60 mg/kg/wk
met
pioglitazone
Ab14 20 mg/kg/wk + met
Ab14 60 mg/kg/wk + met
A
HOMA-IR
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
#
#
#
B
Blood glucose (mg/dL)
250
200
150
100
50
0
#
C
Plasma insulin (μU/mL)
350
300
250
200
150
100
50
0
#
#
#
D
Body weigh (g)
350
300
250
200
150
100
50
0
#
#
#

FIG. 19A

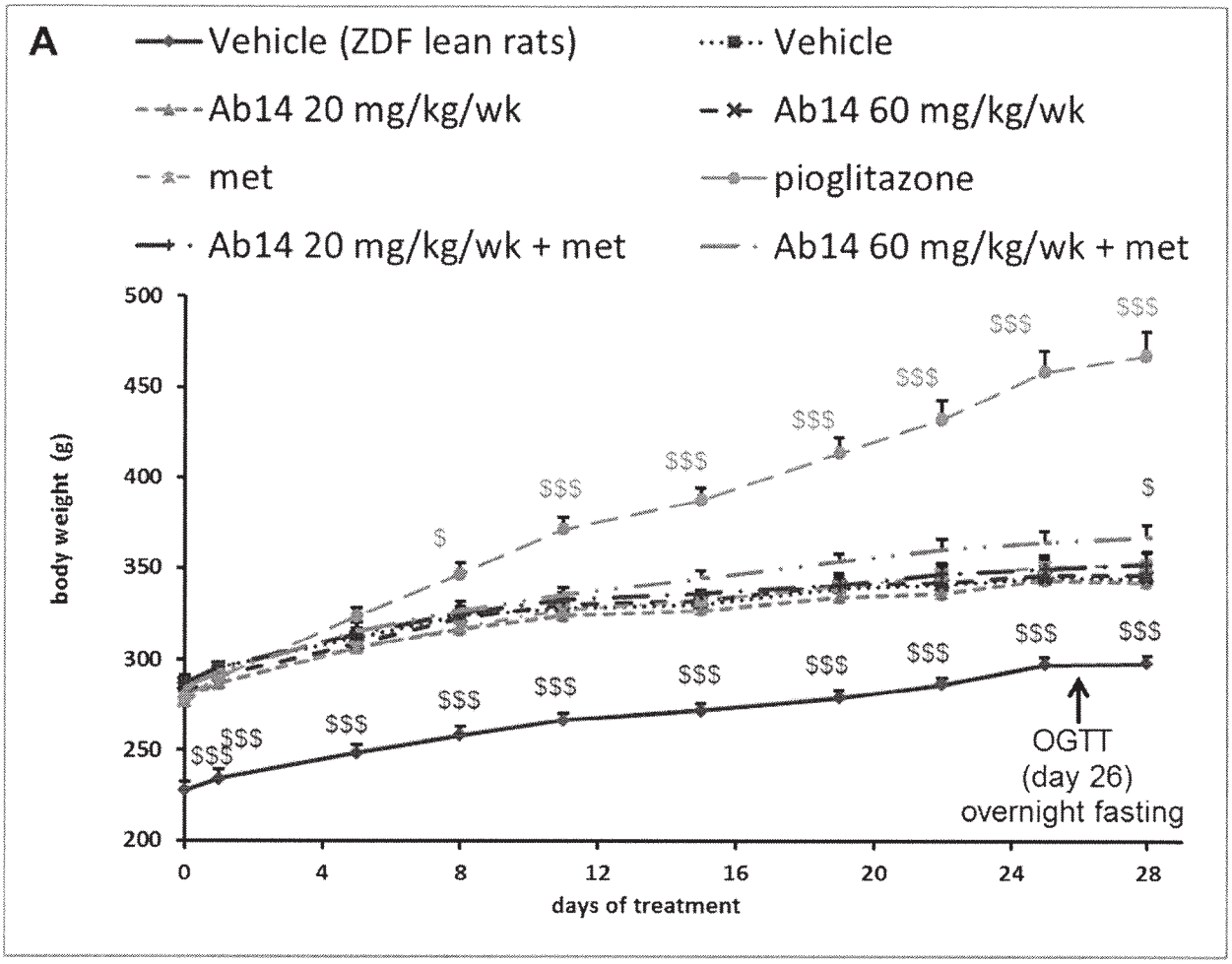

A
Vehicle (ZDF lean rats)
Vehicle
Ab14 20 mg/kg/wk
Ab14 60 mg/kg/wk
met
pioglitazone
Ab14 20 mg/kg/wk + met
Ab14 60 mg/kg/wk + met
body weight (g)
500
450
400
350
300
250
200
0
4
8
12
16
20
24
28
days of treatment
$
$$$
OGTT
(day 26)
overnight fasting

FIG. 19B

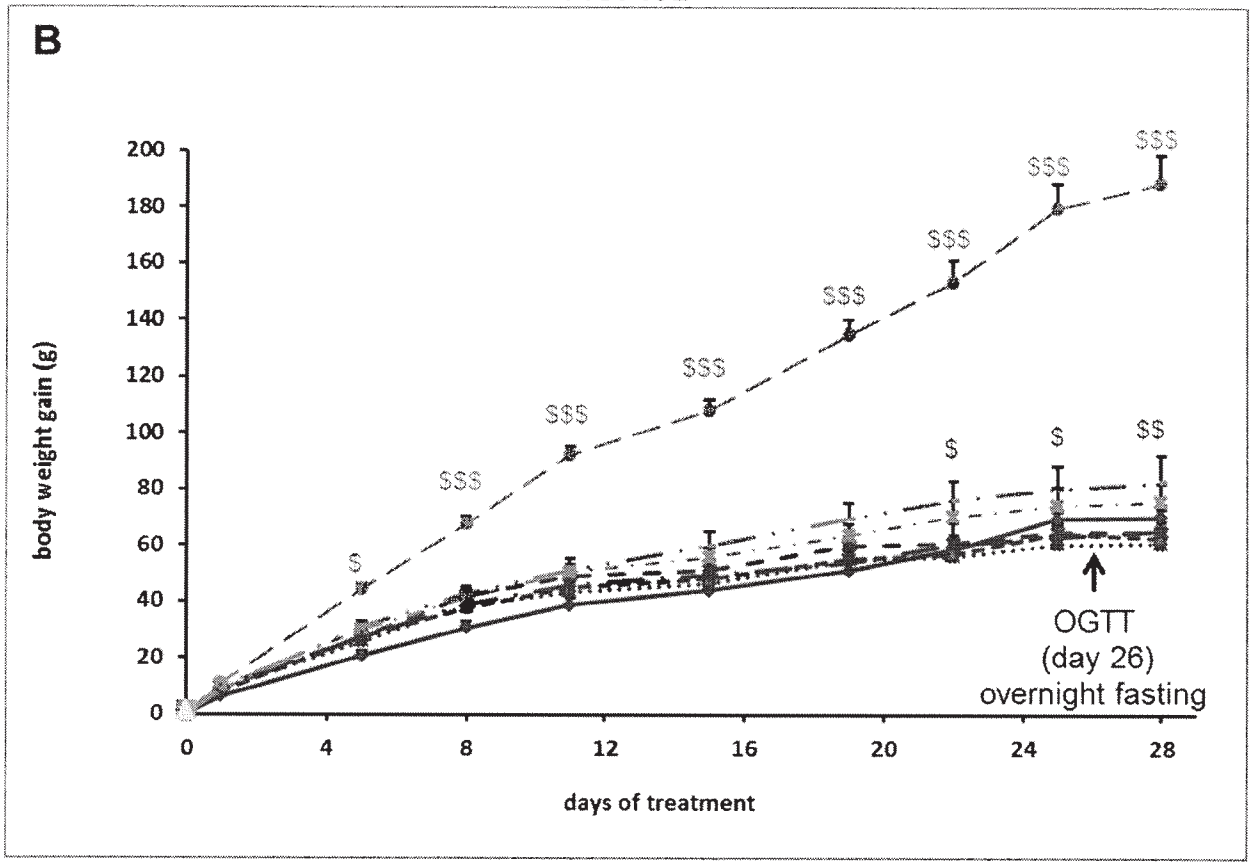

B
body weight gain (g)
200
180
160
140
120
100
80
60
40
20
0
0
4
8
12
16
20
24
28
days of treatment
$
$$$
$$$
$$$
$$$
$$$
$
$
$$
OGTT
(day 26)
overnight fasting

FIG. 20A

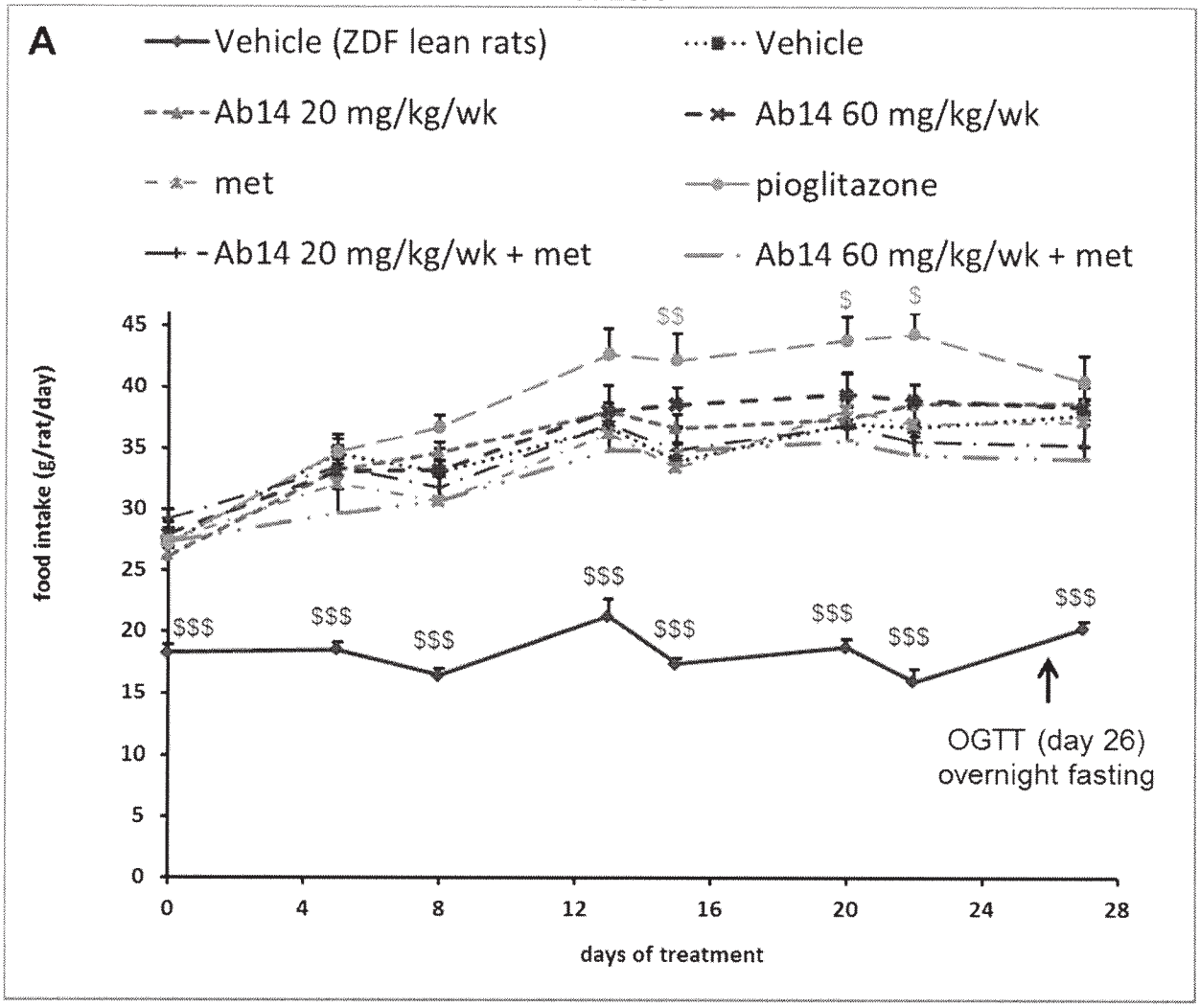
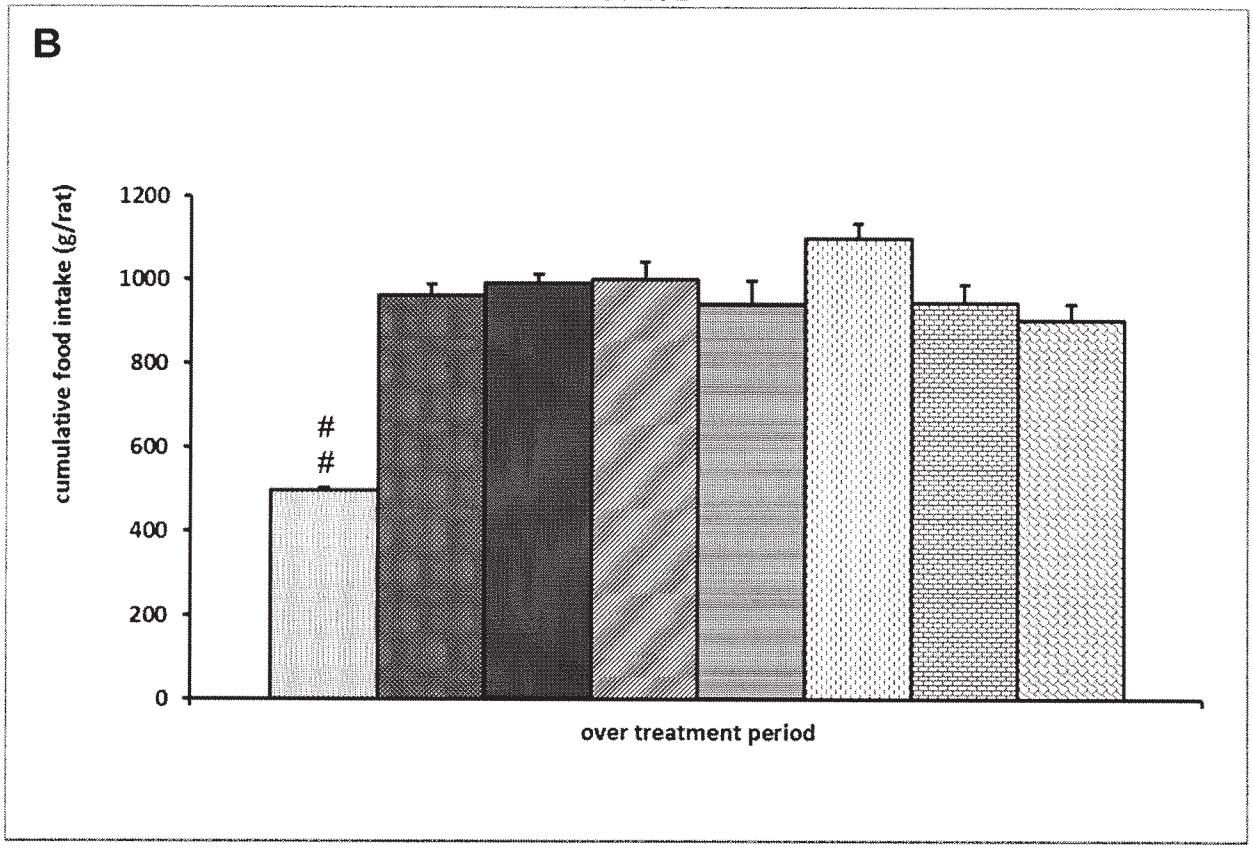
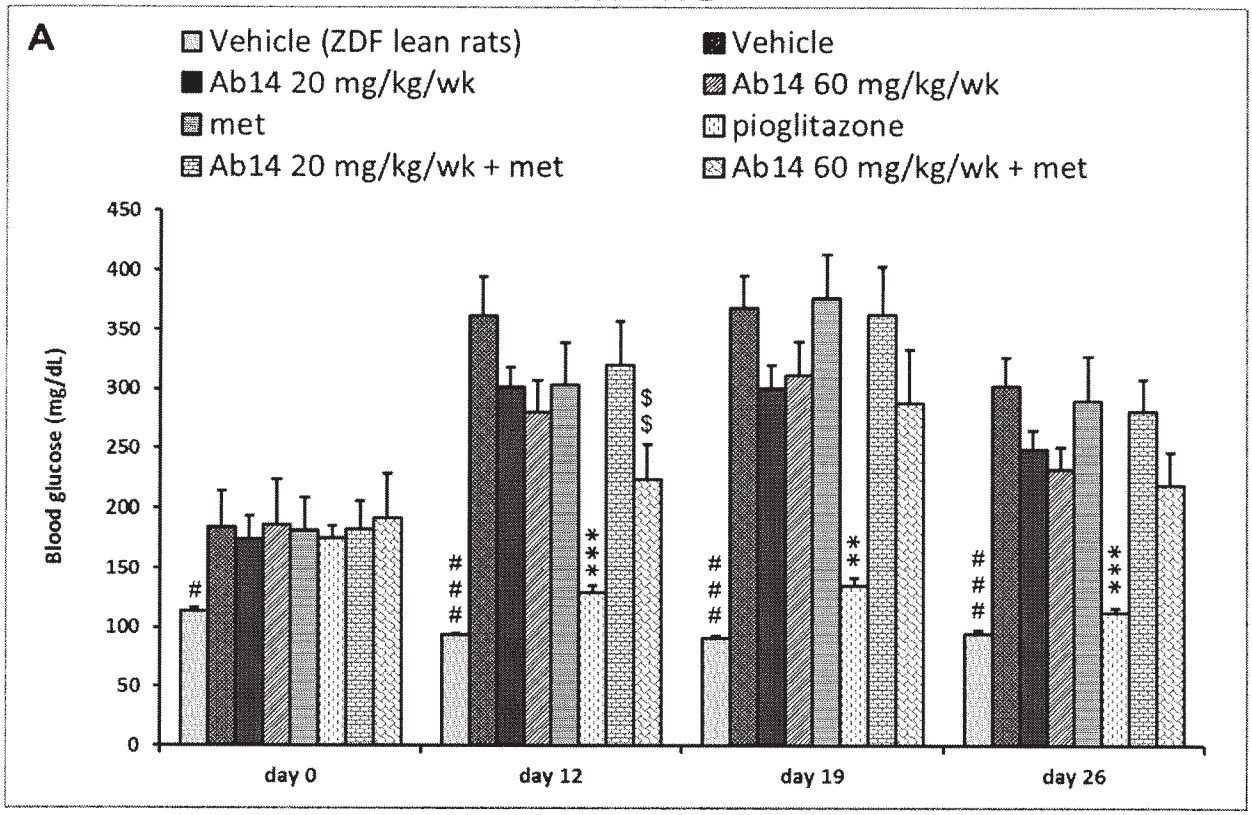
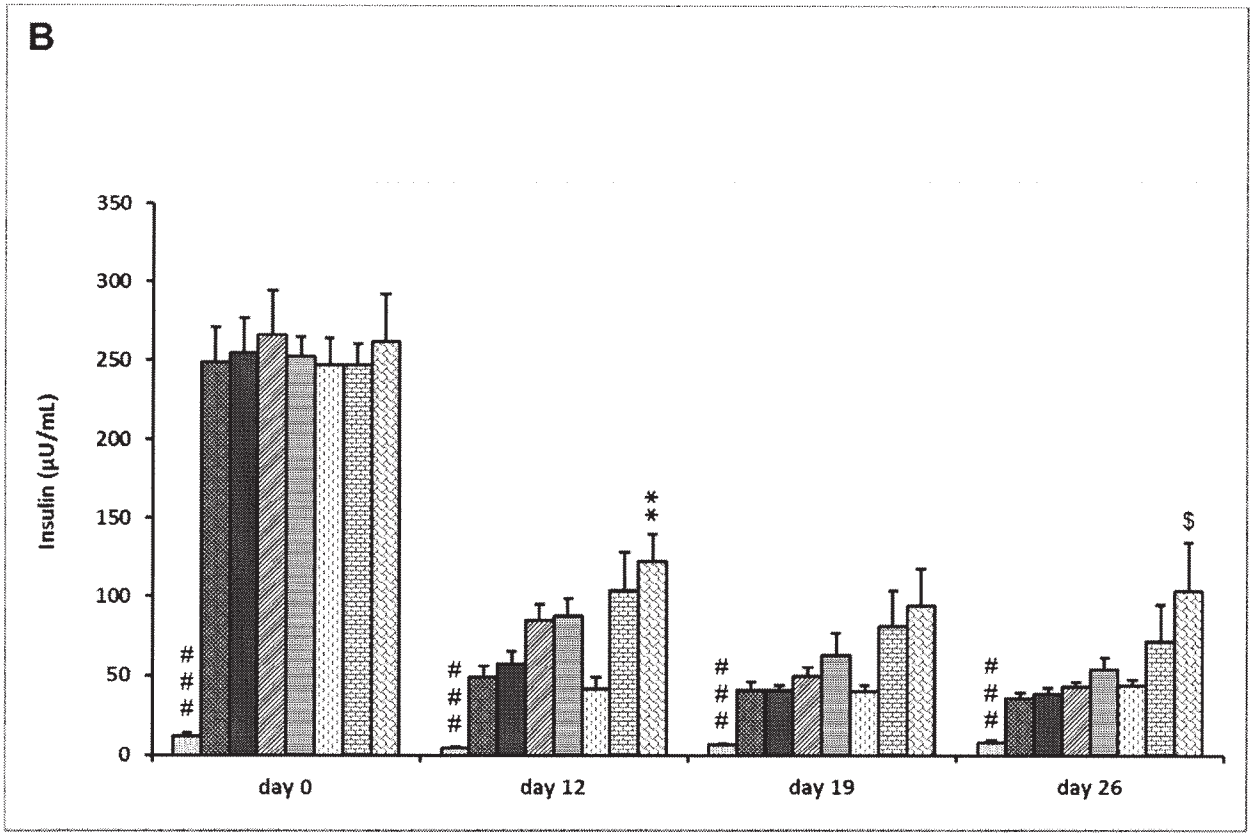

A
Vehicle (ZDF lean rats)
Vehicle
Ab14 20 mg/kg/wk
Ab14 60 mg/kg/wk
met
pioglitazone
Ab14 20 mg/kg/wk + met
Ab14 60 mg/kg/wk + met
food intake (g/rat/day)
days of treatment
OGTT (day 26)
overnight fasting
$
$$
$$$

FIG. 20B

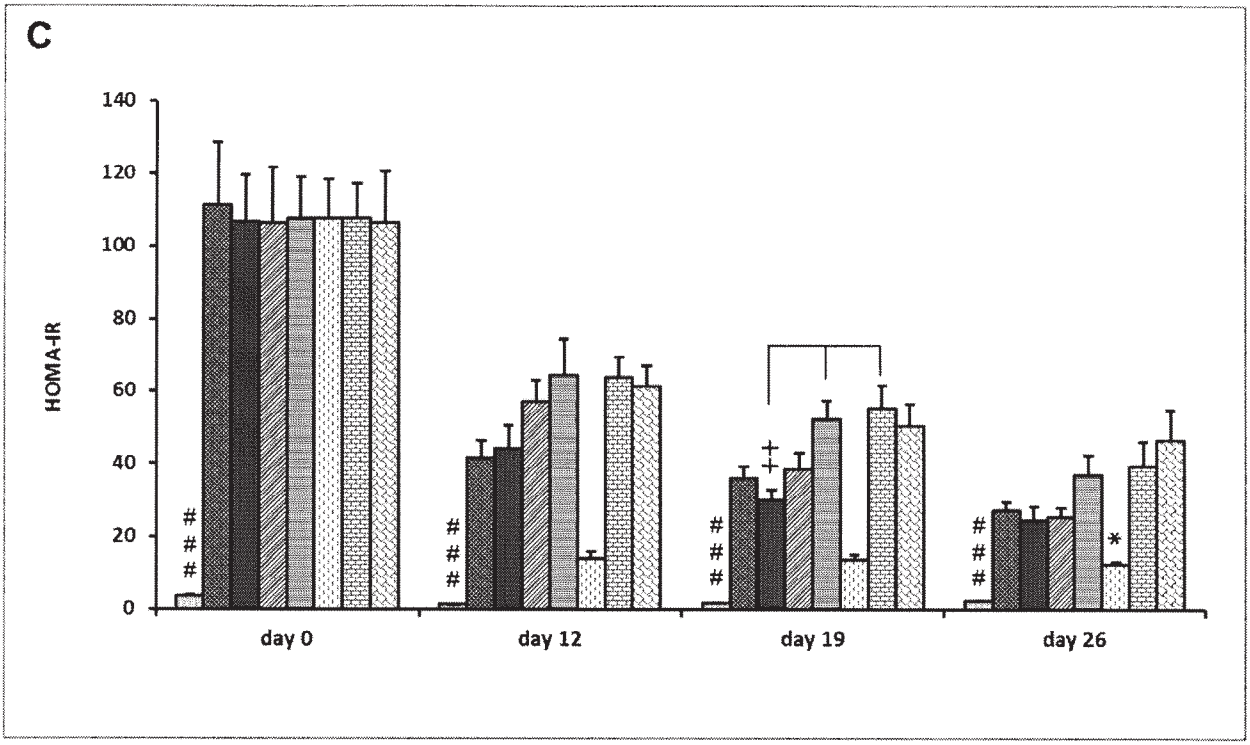

B
cumulative food intake (g/rat)
1200
1000
800
600
400
200
0
#
#
over treatment period

FIGS. 21A-B


A
Vehicle (ZDF lean rats)
Vehicle
Ab14 20 mg/kg/wk
Ab14 60 mg/kg/wk
met
pioglitazone
Ab14 20 mg/kg/wk + met
Ab14 60 mg/kg/wk + met
Blood glucose (mg/dL)
450
400
350
300
250
200
150
100
50
0
day 0
day 12
day 19
day 26


B
Insulin (µU/mL)
350
300
250
200
150
100
50
0
day 0
day 12
day 19
day 26

FIGS. 21C-D


C
HOMA-IR
140
120
100
80
60
40
20
0
day 0
day 12
day 19
day 26

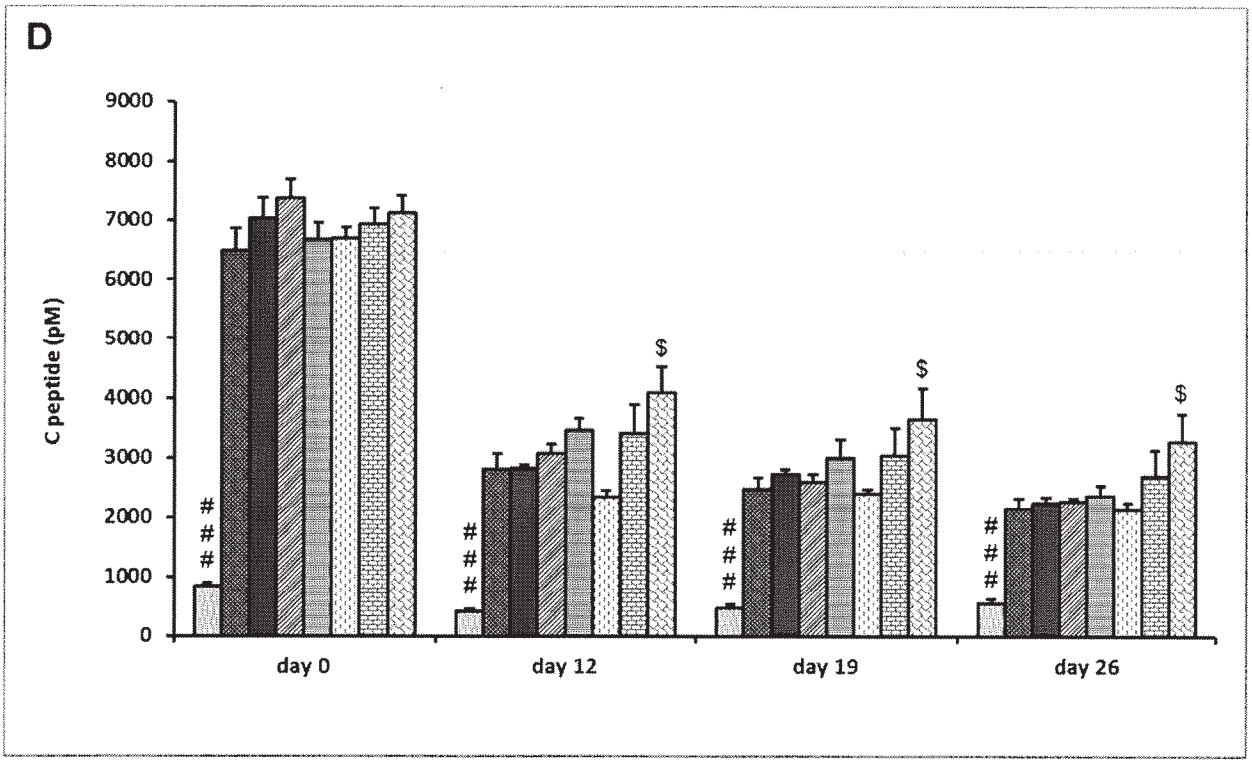

D
C peptide (pM)
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
day 0
day 12
day 19
day 26

FIG. 22

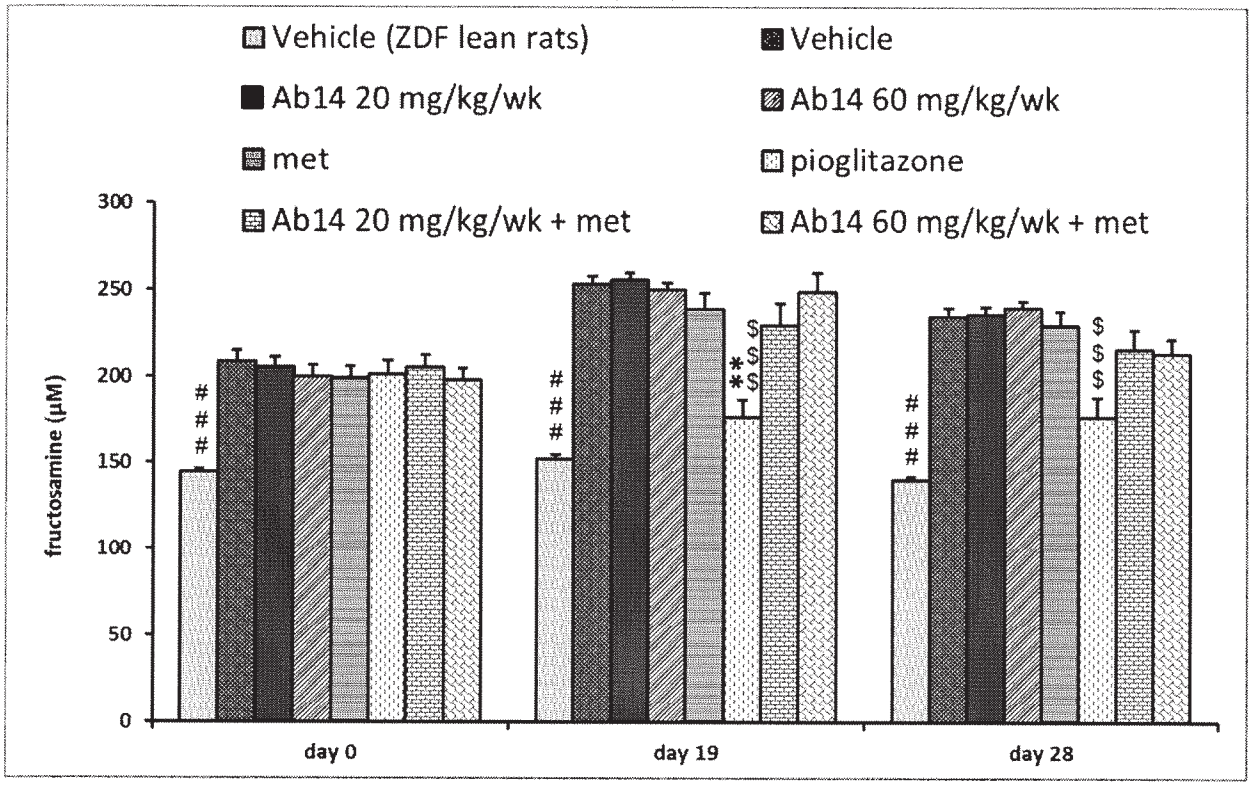

Vehicle (ZDF lean rats)
Vehicle
Ab14 20 mg/kg/wk
Ab14 60 mg/kg/wk
met
pioglitazone
Ab14 20 mg/kg/wk + met
Ab14 60 mg/kg/wk + met
fructosamine (μM)
300
250
200
150
100
50
0
day 0
day 19
day 28

FIG. 23

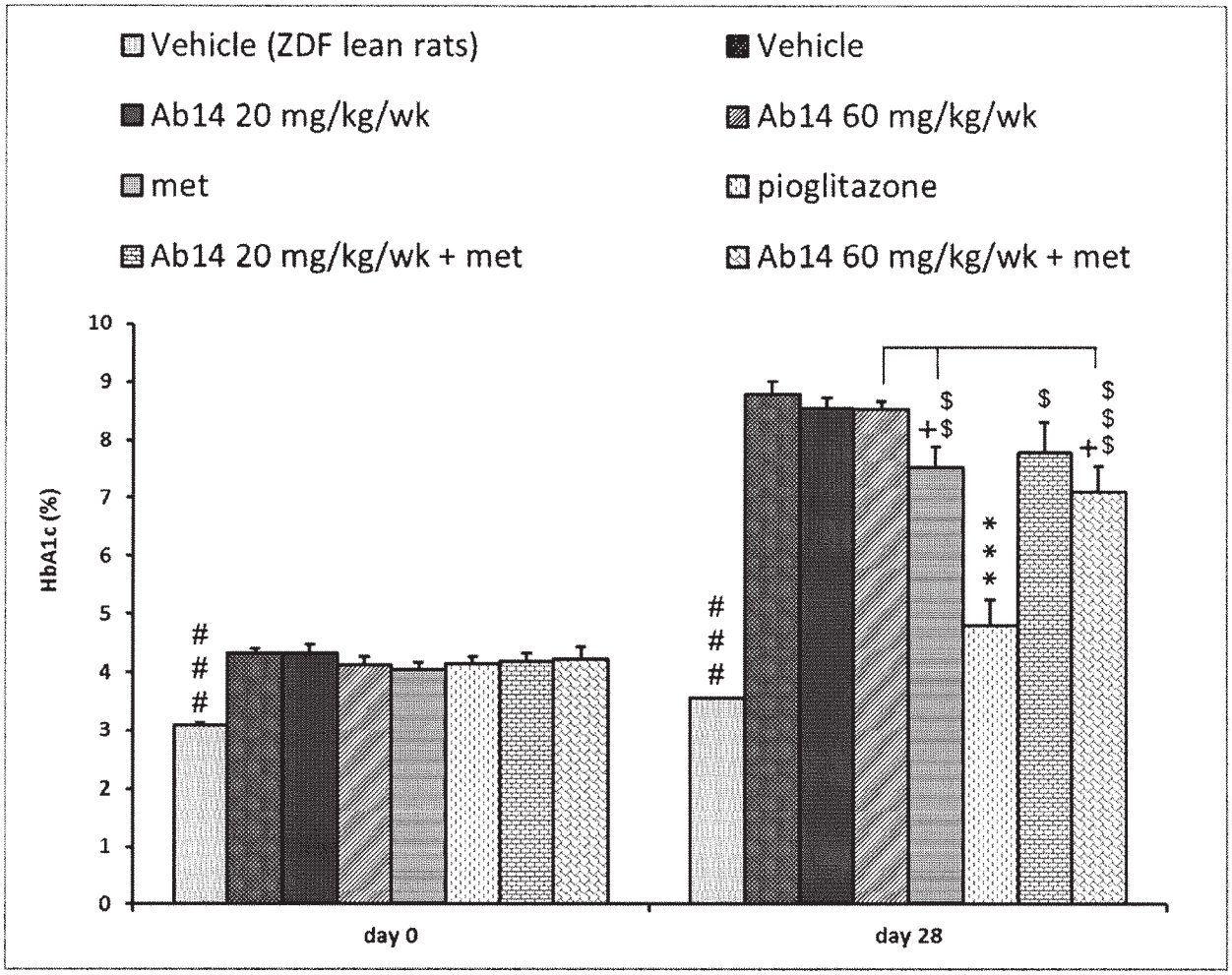

Vehicle (ZDF lean rats)
Vehicle
Ab14 20 mg/kg/wk
Ab14 60 mg/kg/wk
met
pioglitazone
Ab14 20 mg/kg/wk + met
Ab14 60 mg/kg/wk + met
HbA1c (%)
10
9
8
7
6
5
4
3
2
1
0
day 0
day 28

FIG. 24

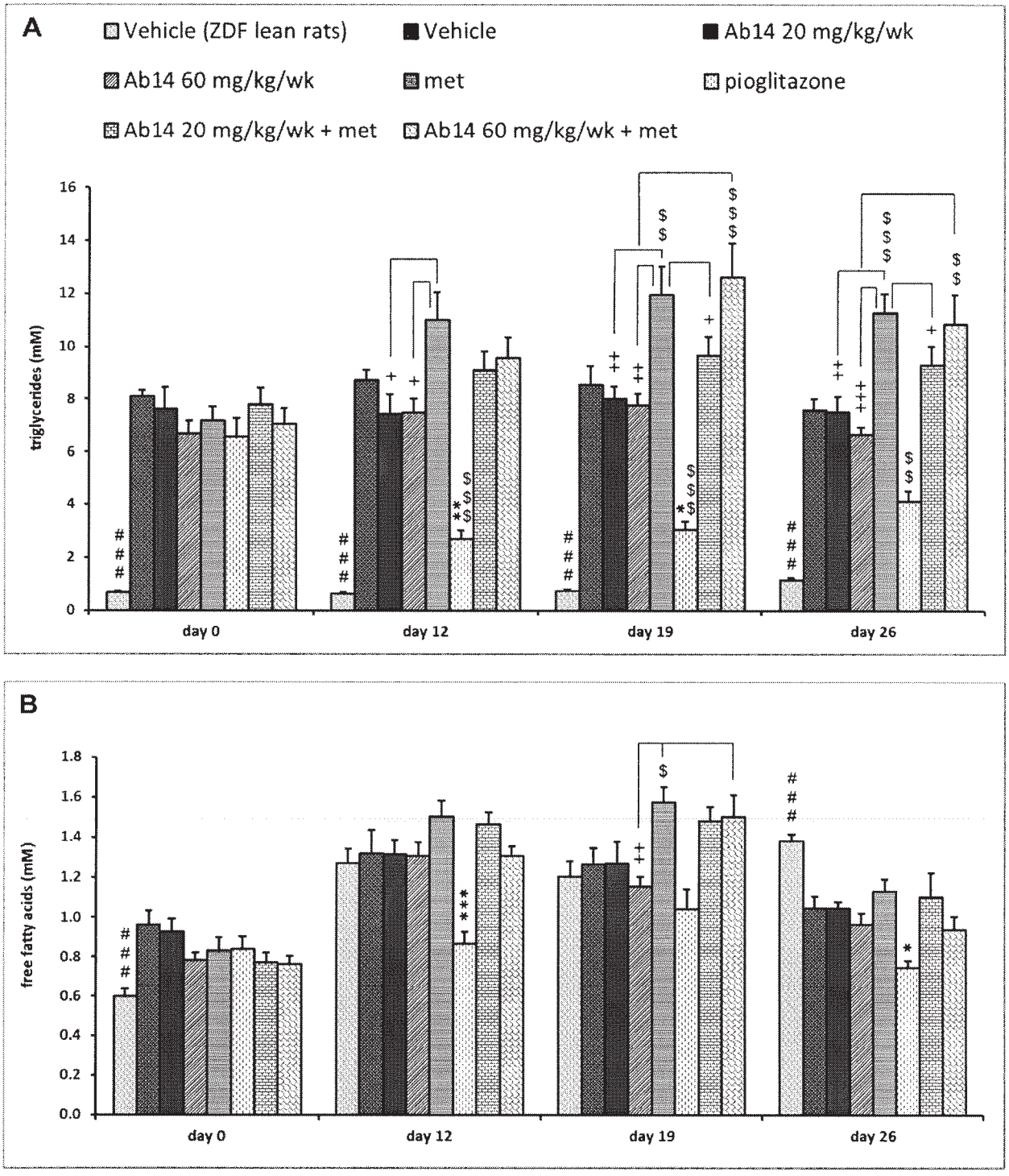

A
Vehicle (ZDF lean rats)
Vehicle
Ab14 20 mg/kg/wk
Ab14 60 mg/kg/wk
met
pioglitazone
Ab14 20 mg/kg/wk + met
Ab14 60 mg/kg/wk + met
triglycerides (mM)
day 0
day 12
day 19
day 26
B
free fatty acids (mM)
day 0
day 12
day 19
day 26

FIG. 25A

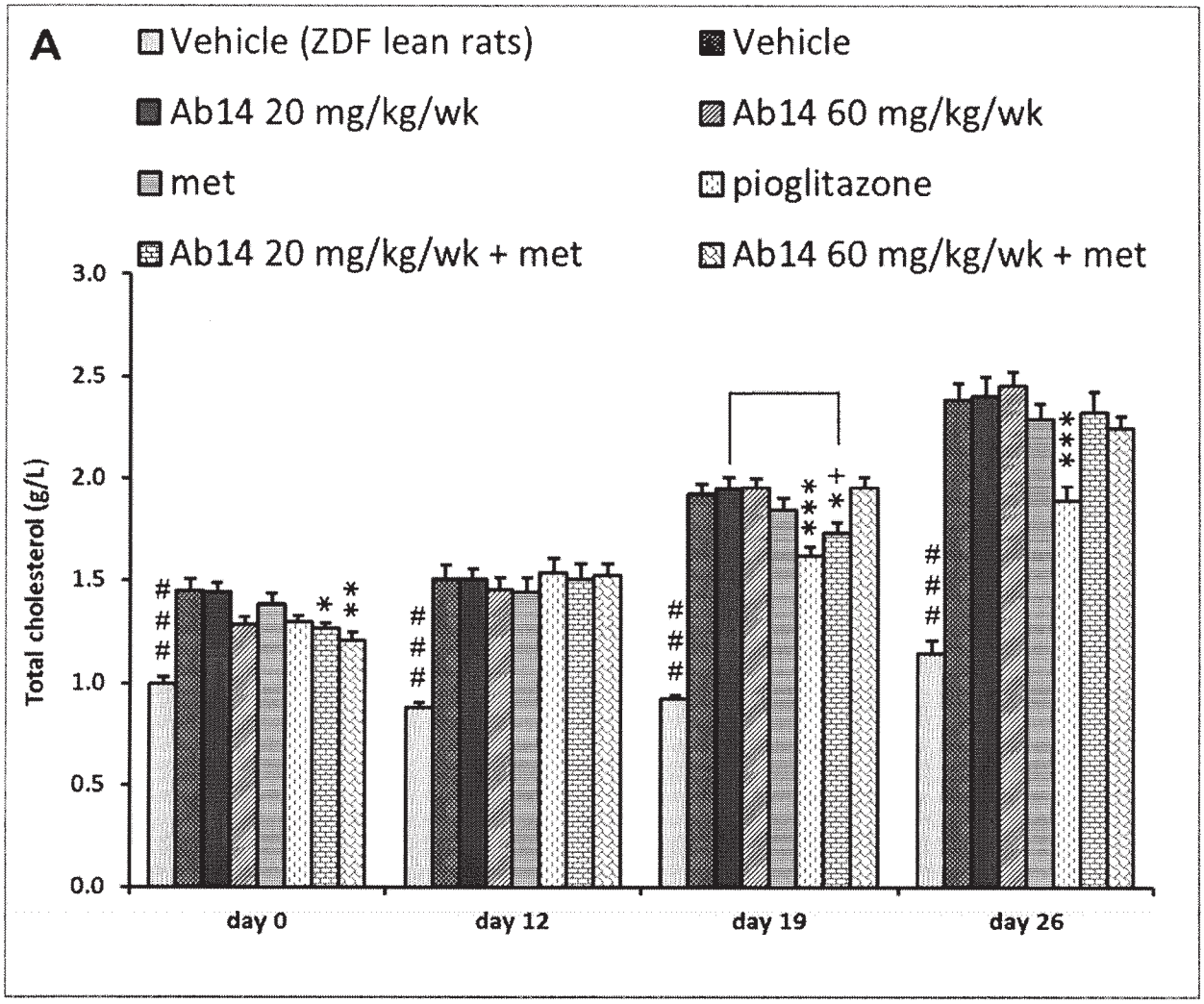

A
Vehicle (ZDF lean rats)
Vehicle
Ab14 20 mg/kg/wk
Ab14 60 mg/kg/wk
met
pioglitazone
Ab14 20 mg/kg/wk + met
Ab14 60 mg/kg/wk + met
Total cholesterol (g/L)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
day 0
day 12
day 19
day 26

FIG. 25B

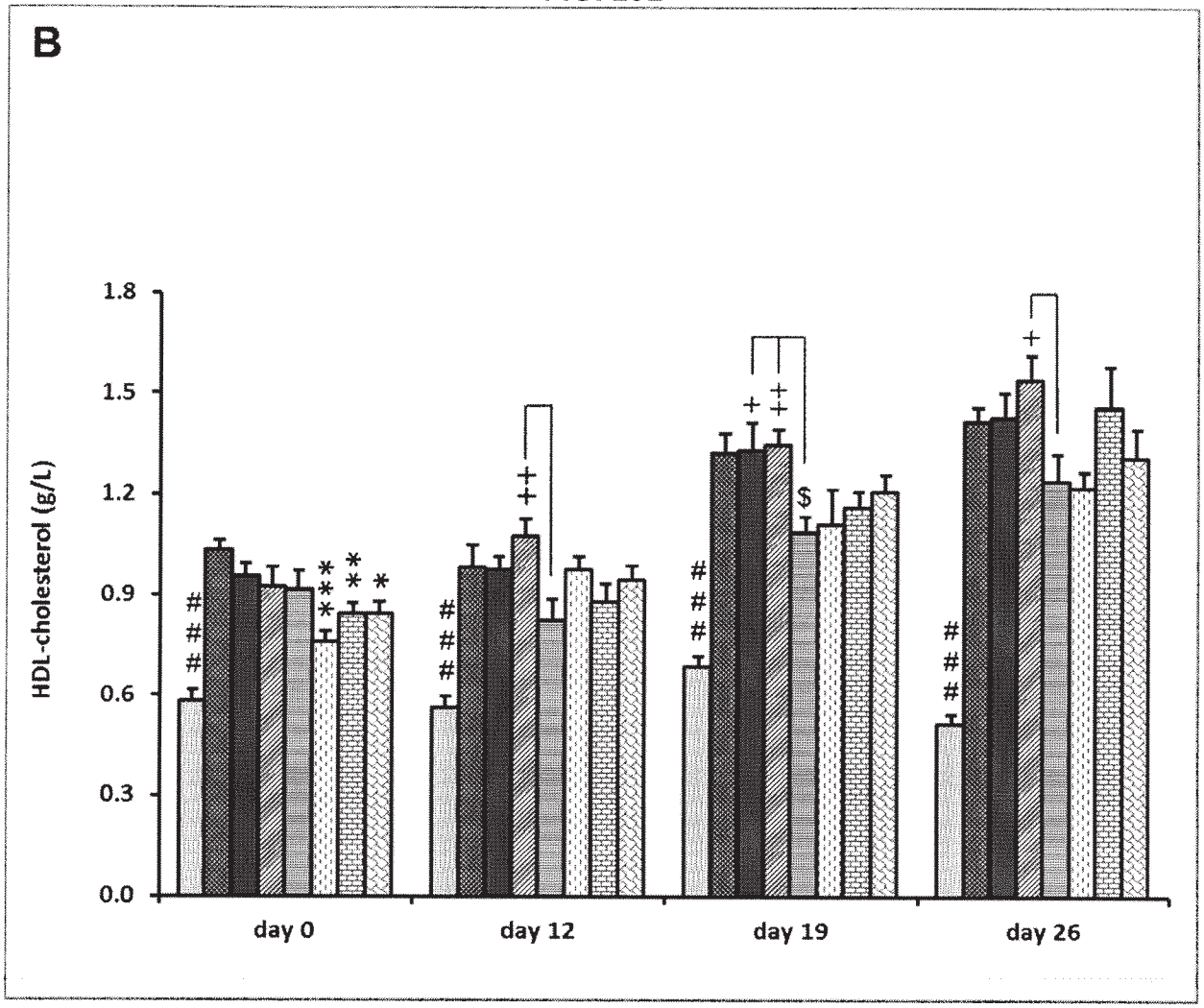

B
HDL-cholesterol (g/L)
1.8
1.5
1.2
0.9
0.6
0.3
0.0
day 0
day 12
day 19
day 26

FIG. 25C

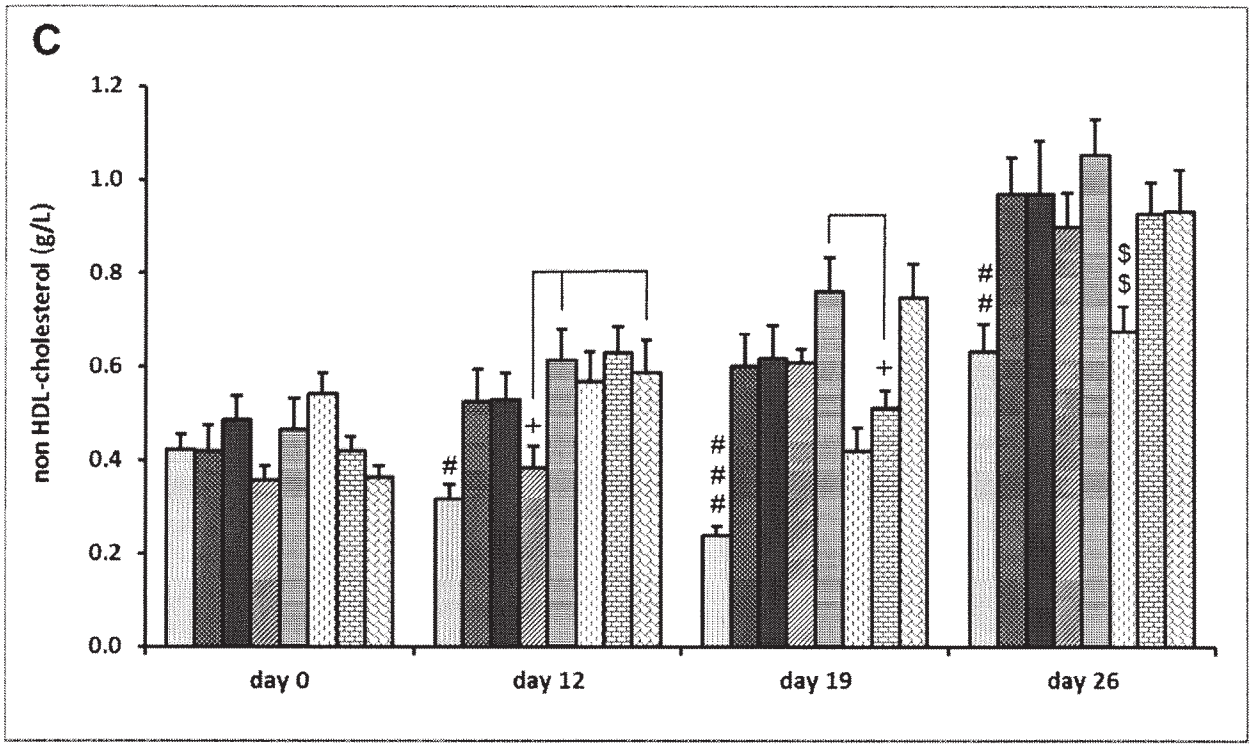

C
non HDL-cholesterol (g/L)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
day 0
day 12
day 19
day 26
#
+
#
#
#
+
#
#
$
$

FIG. 26A

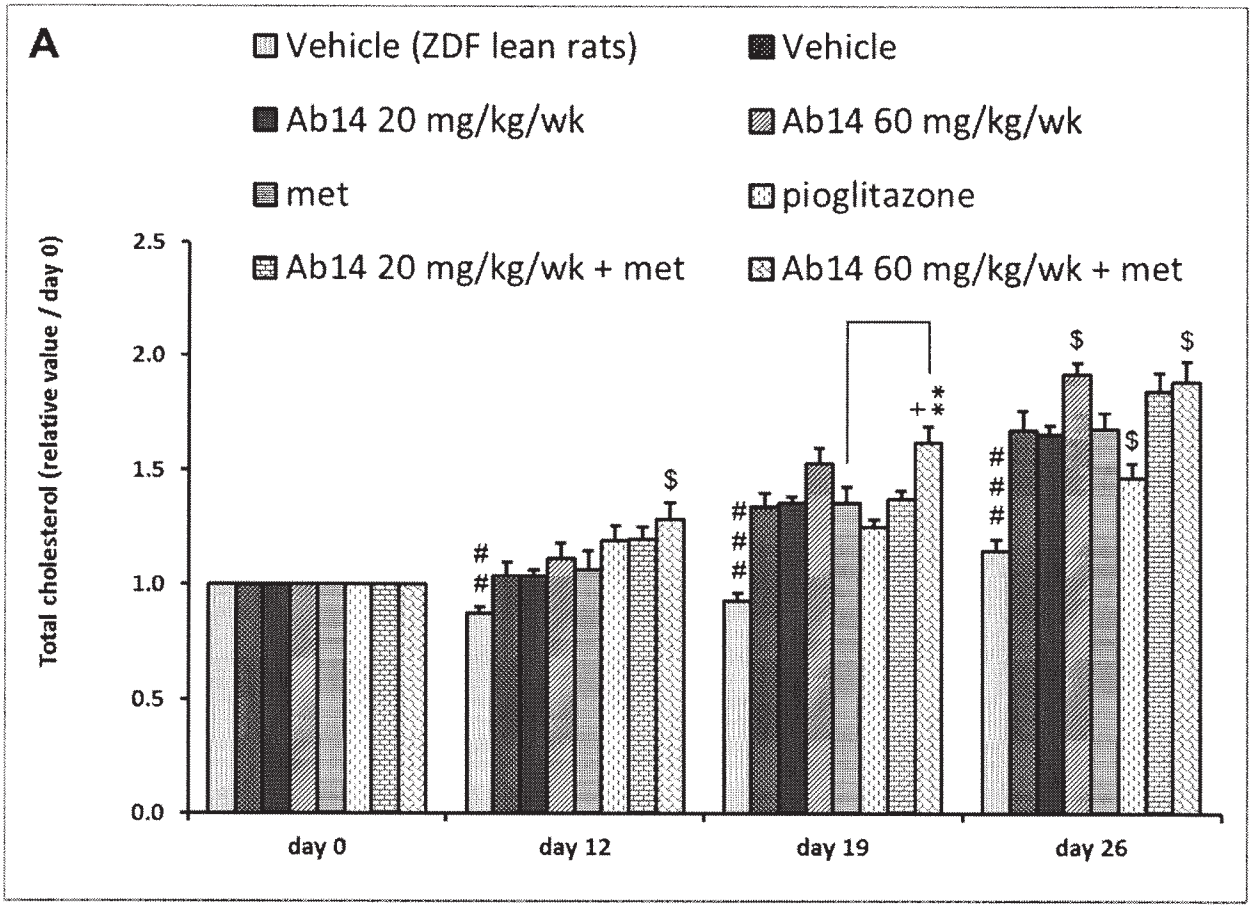

A
Vehicle (ZDF lean rats)
Vehicle
Ab14 20 mg/kg/wk
Ab14 60 mg/kg/wk
met
pioglitazone
Ab14 20 mg/kg/wk + met
Ab14 60 mg/kg/wk + met
Total cholesterol (relative value / day 0)
2.5
2.0
1.5
1.0
0.5
0.0
day 0
day 12
day 19
day 26

FIG. 26B

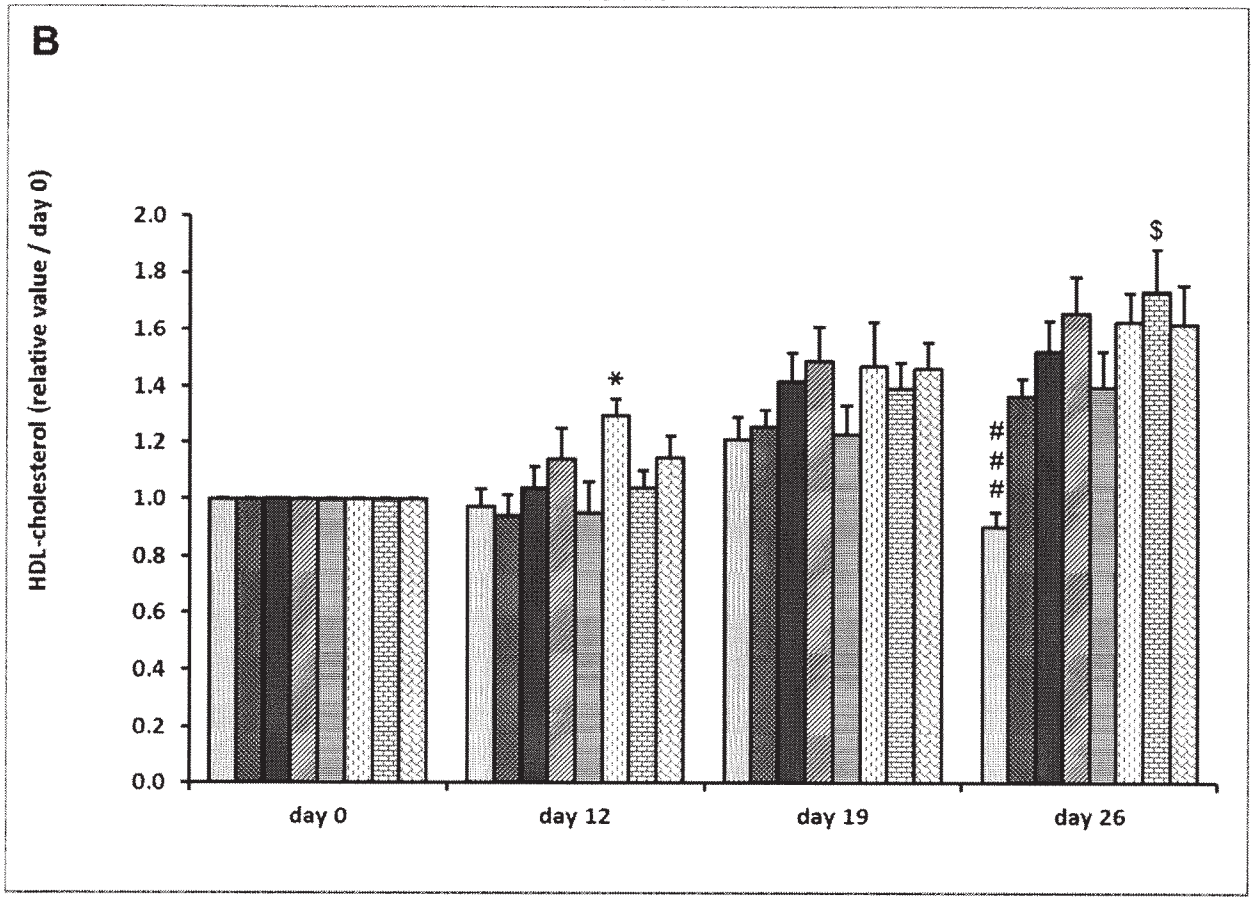

B
HDL-cholesterol (relative value / day 0)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
*
#
#
#
$
day 0
day 12
day 19
day 26

FIG. 26C

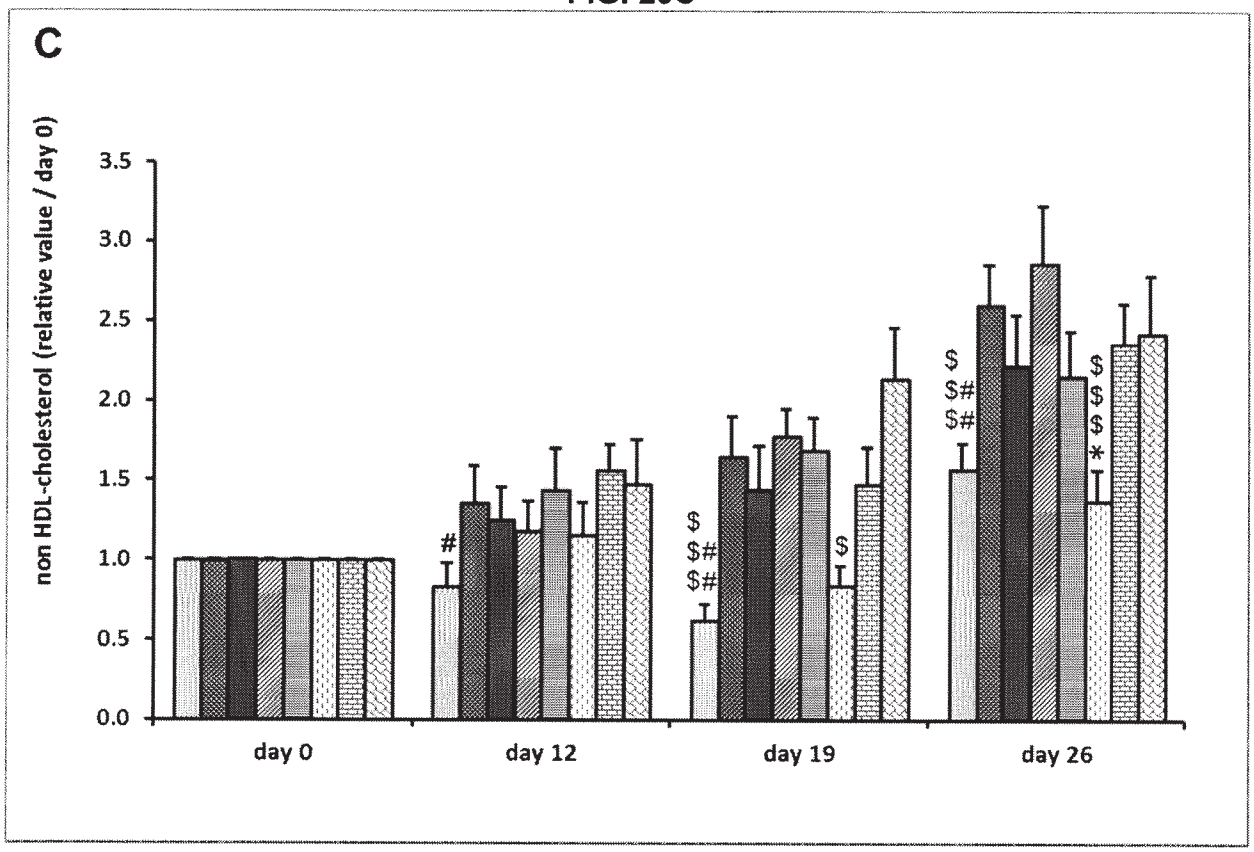

C
non HDL-cholesterol (relative value / day 0)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
day 0
day 12
day 19
day 26

FIG. 27A

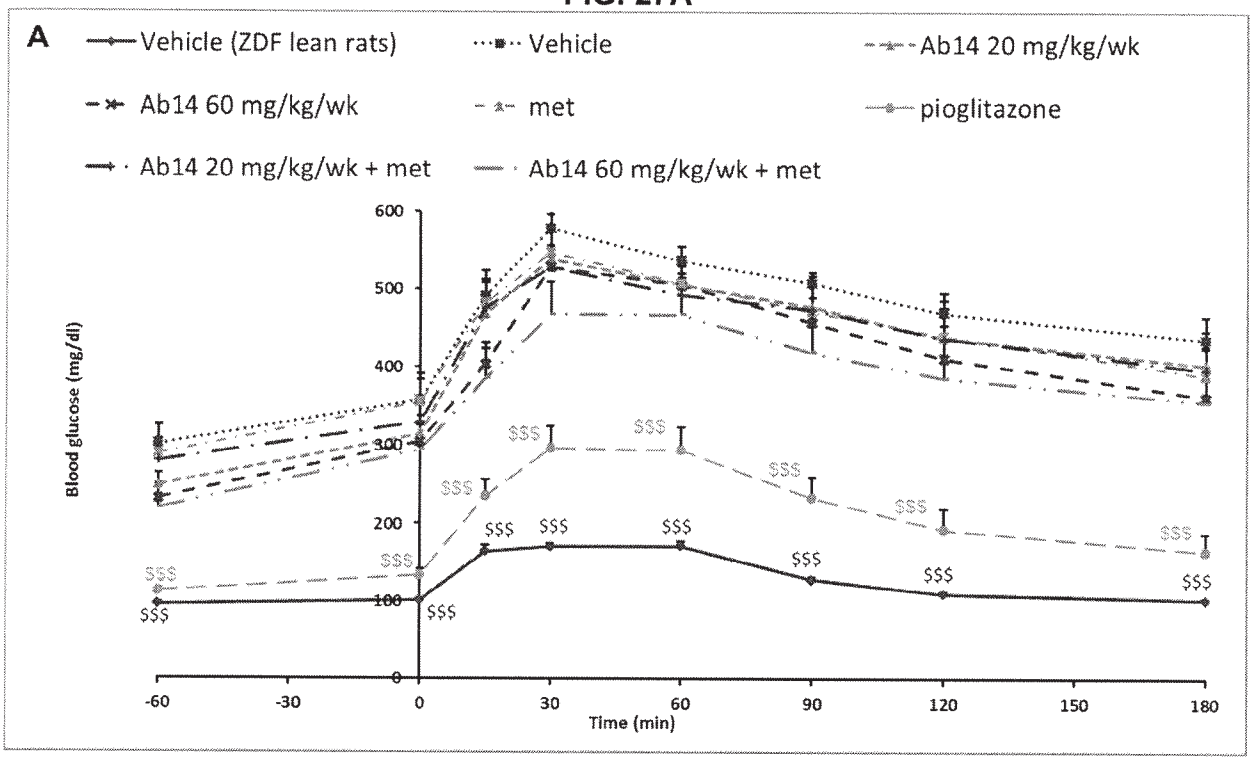

A
Vehicle (ZDF lean rats)
Vehicle
Ab14 20 mg/kg/wk
Ab14 60 mg/kg/wk
met
pioglitazone
Ab14 20 mg/kg/wk + met
Ab14 60 mg/kg/wk + met
Blood glucose (mg/dl)
600
500
400
300
200
100
0
$$$
-60
-30
0
30
60
90
120
150
180
Time (min)

FIG. 27B

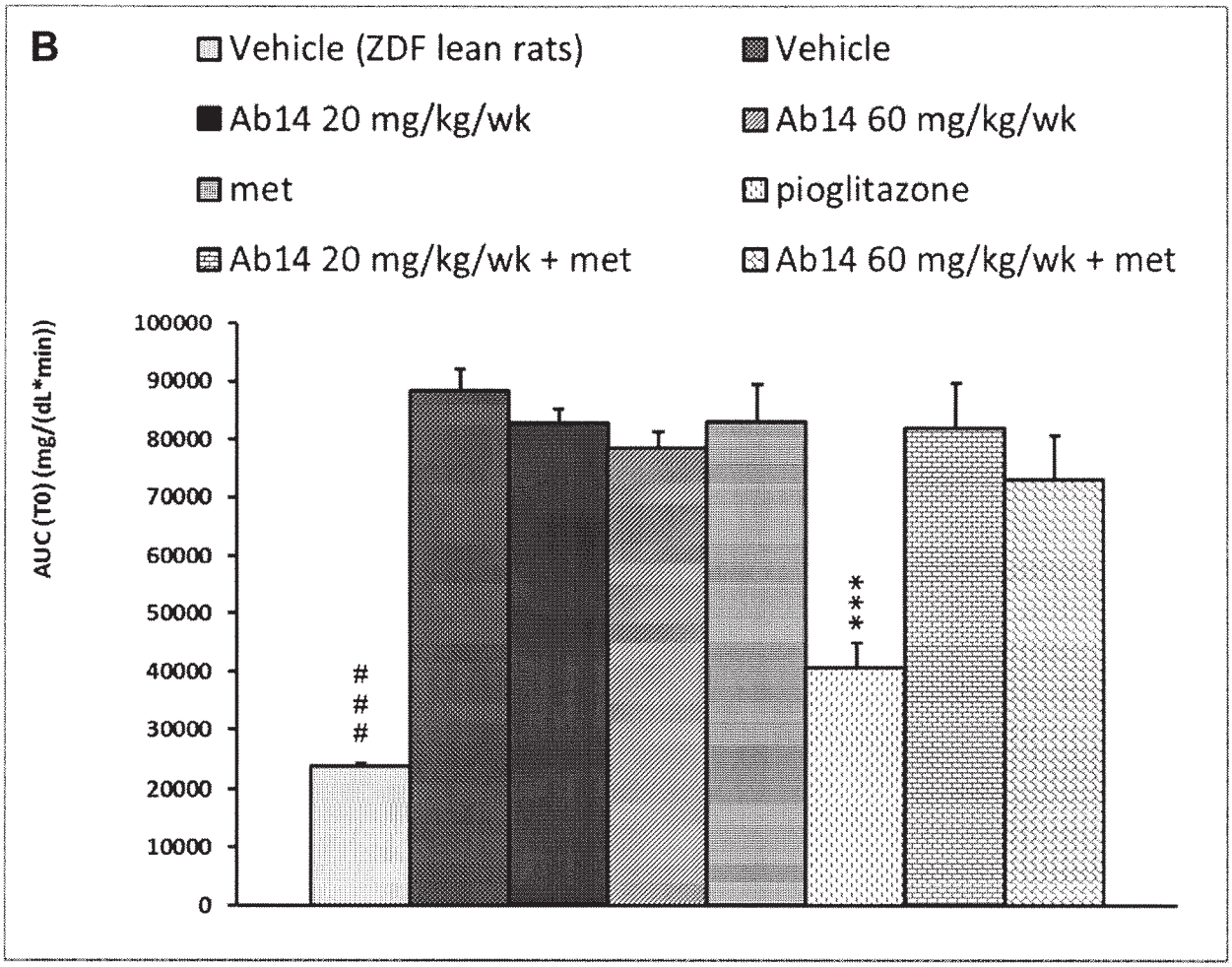

B
Vehicle (ZDF lean rats)
Vehicle
Ab14 20 mg/kg/wk
Ab14 60 mg/kg/wk
met
pioglitazone
Ab14 20 mg/kg/wk + met
Ab14 60 mg/kg/wk + met
AUC (T0) (mg/(dL*min))
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
###
***

FIG. 27C

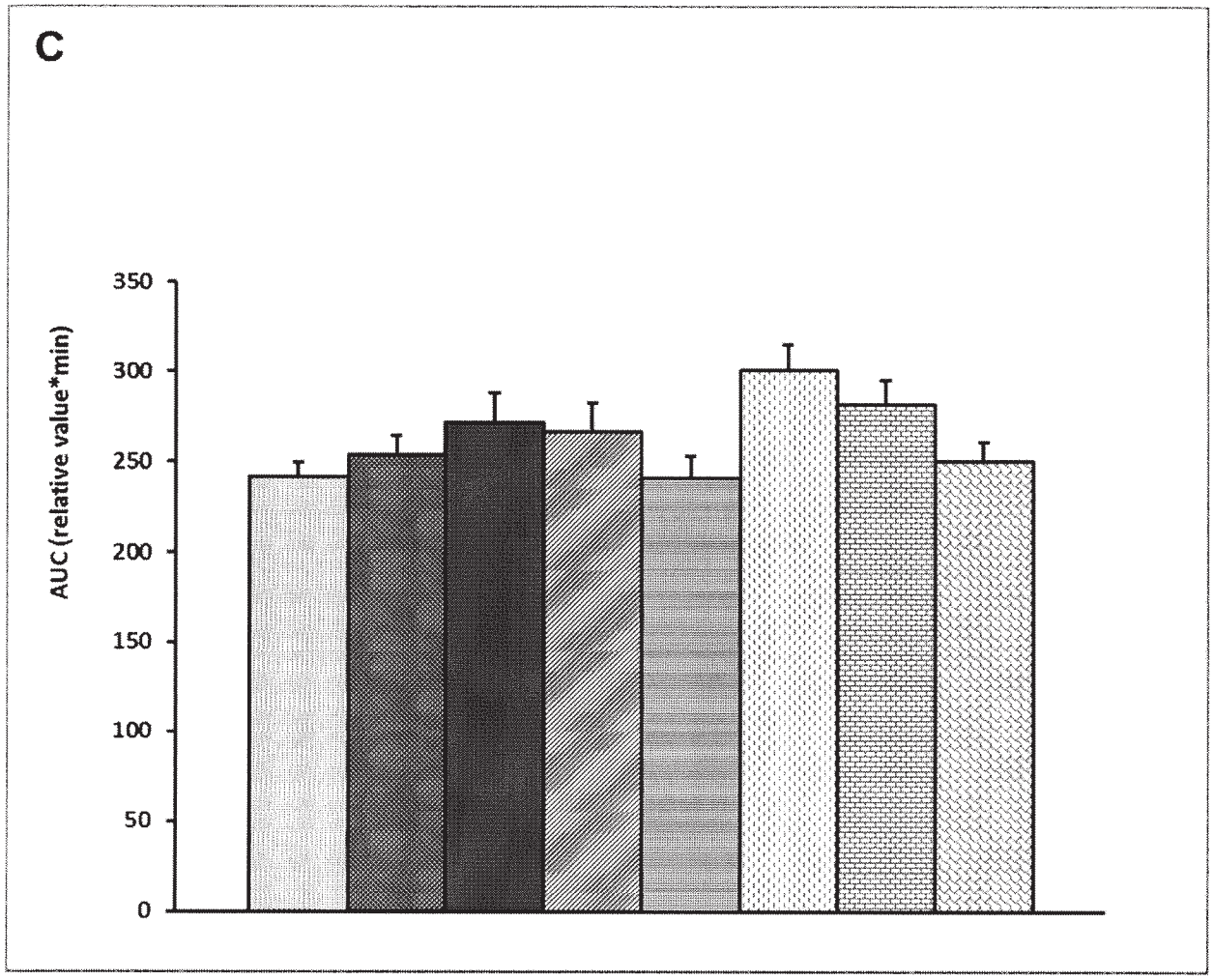


FIG. 28

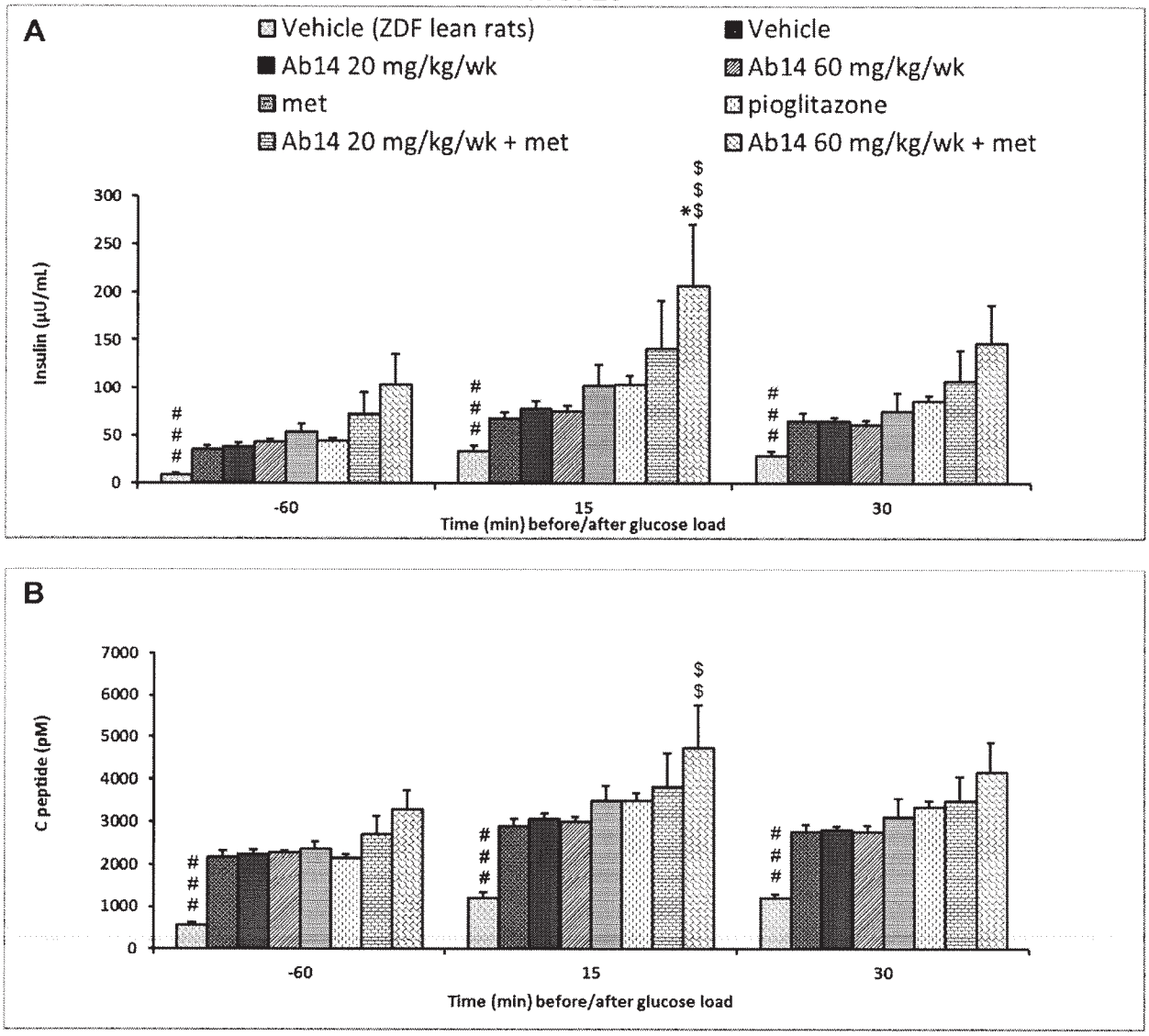
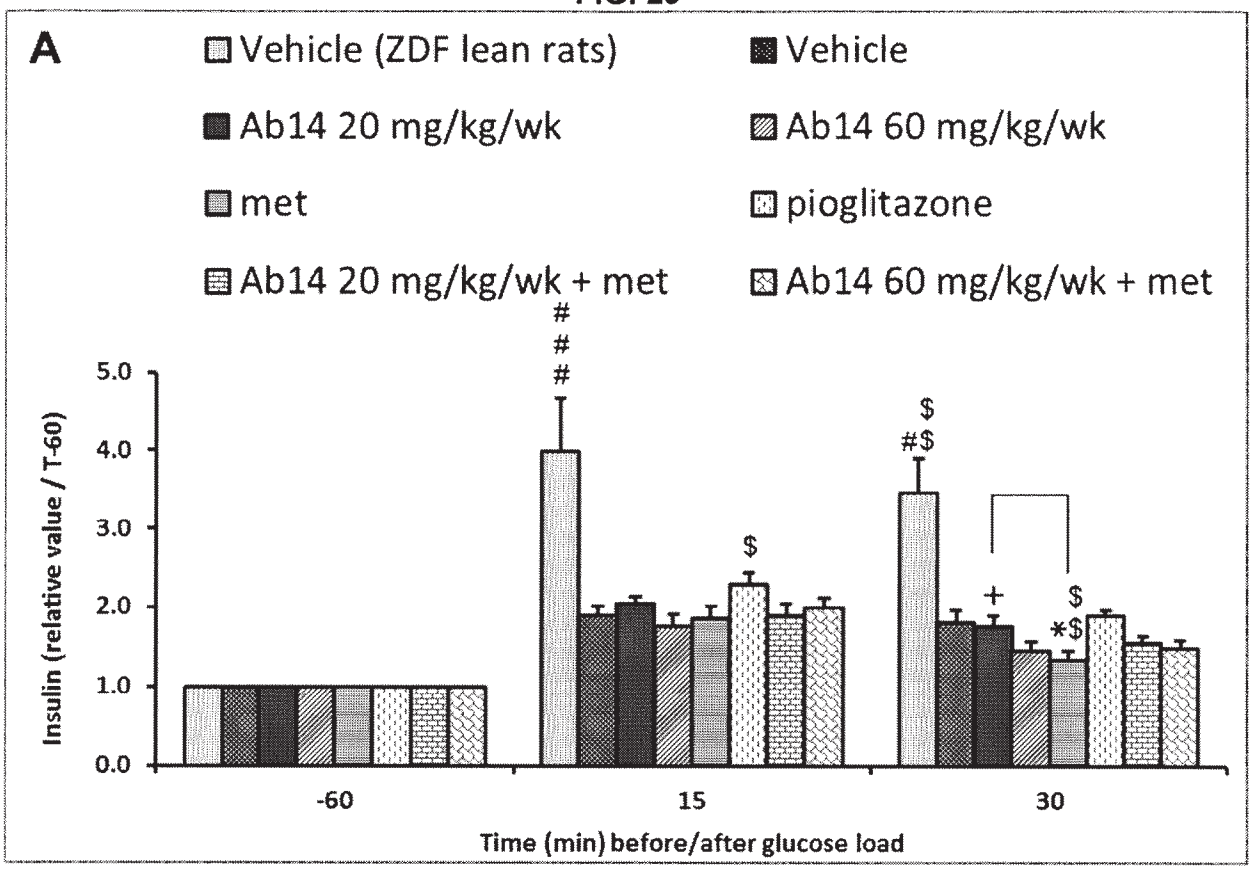
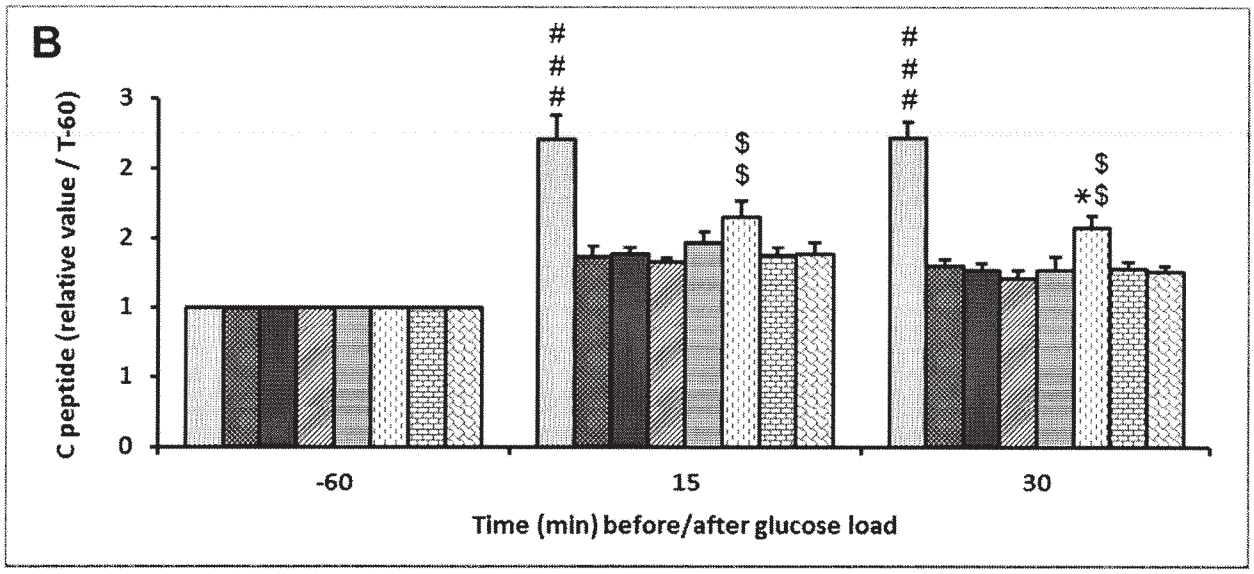
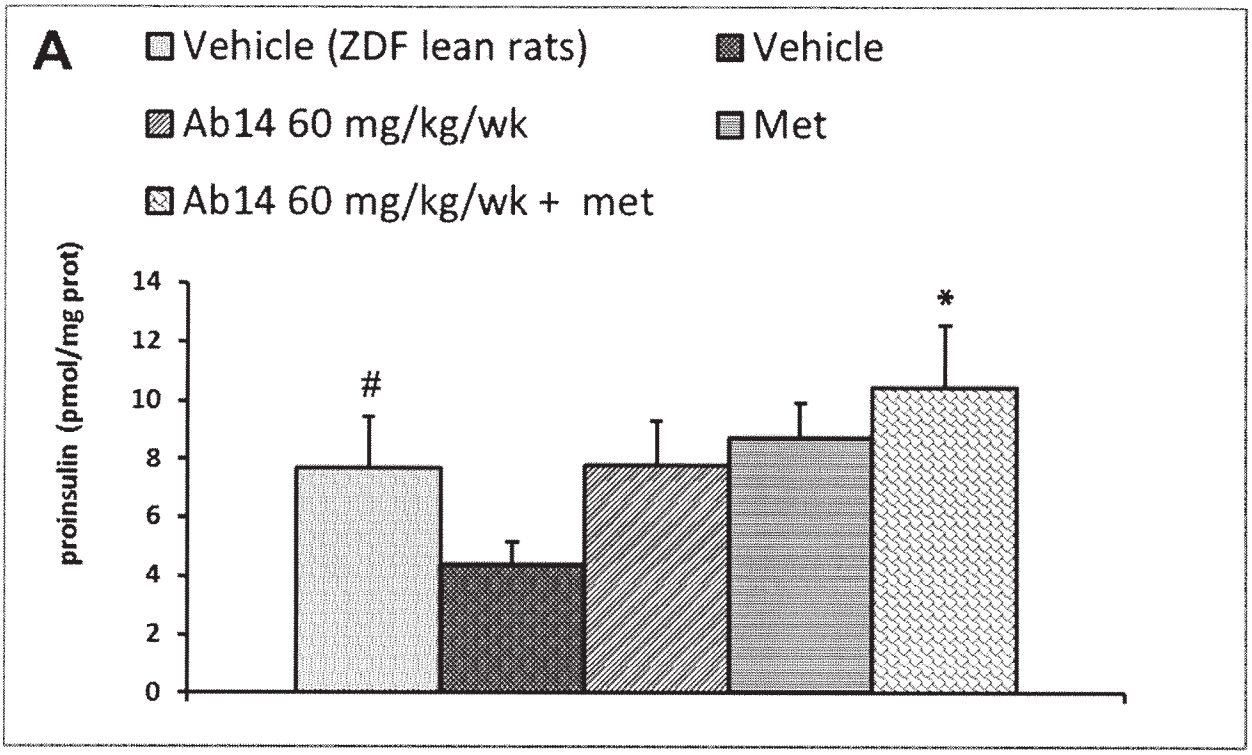

A
Vehicle (ZDF lean rats)
Ab14 20 mg/kg/wk
met
Ab14 20 mg/kg/wk + met
Vehicle
Ab14 60 mg/kg/wk
pioglitazone
Ab14 60 mg/kg/wk + met
Insulin (µU/mL)
300
250
200
150
100
50
0
-60
15
30
Time (min) before/after glucose load
B
C peptide (pM)
7000
6000
5000
4000
3000
2000
1000
0
-60
15
30
Time (min) before/after glucose load

FIG. 29


A
Vehicle (ZDF lean rats)
Vehicle
Ab14 20 mg/kg/wk
Ab14 60 mg/kg/wk
met
pioglitazone
Ab14 20 mg/kg/wk + met
Ab14 60 mg/kg/wk + met
Insulin (relative value / T-60)
5.0
4.0
3.0
2.0
1.0
0.0
-60
15
30
Time (min) before/after glucose load


B
C peptide (relative value / T-60)
3
2
2
1
1
0
-60
15
30
Time (min) before/after glucose load

FIGS. 30A-B


A
Vehicle (ZDF lean rats)
Vehicle
Ab14 60 mg/kg/wk
Met
Ab14 60 mg/kg/wk + met
proinsulin (pmol/mg prot)
14
12
10
8
6
4
2
0
#
*

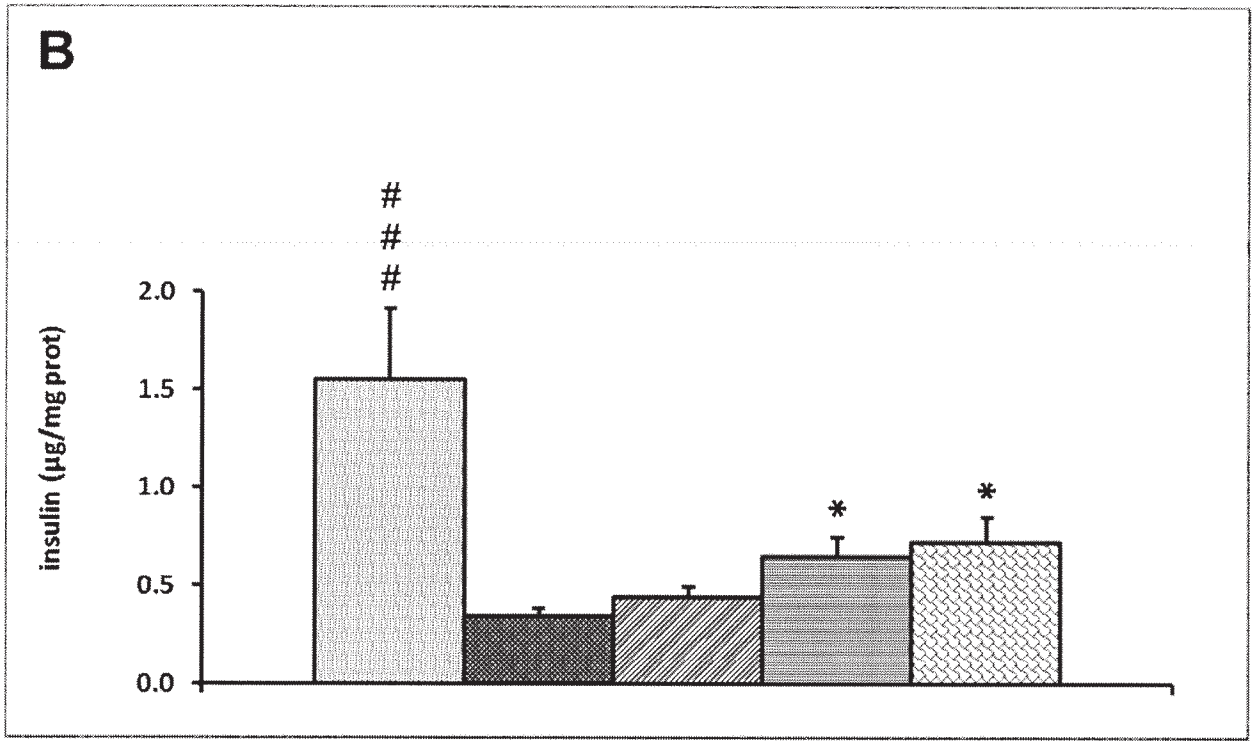

B
insulin (µg/mg prot)
2.0
1.5
1.0
0.5
0.0
#
#
#
*
*

FIG. 30C

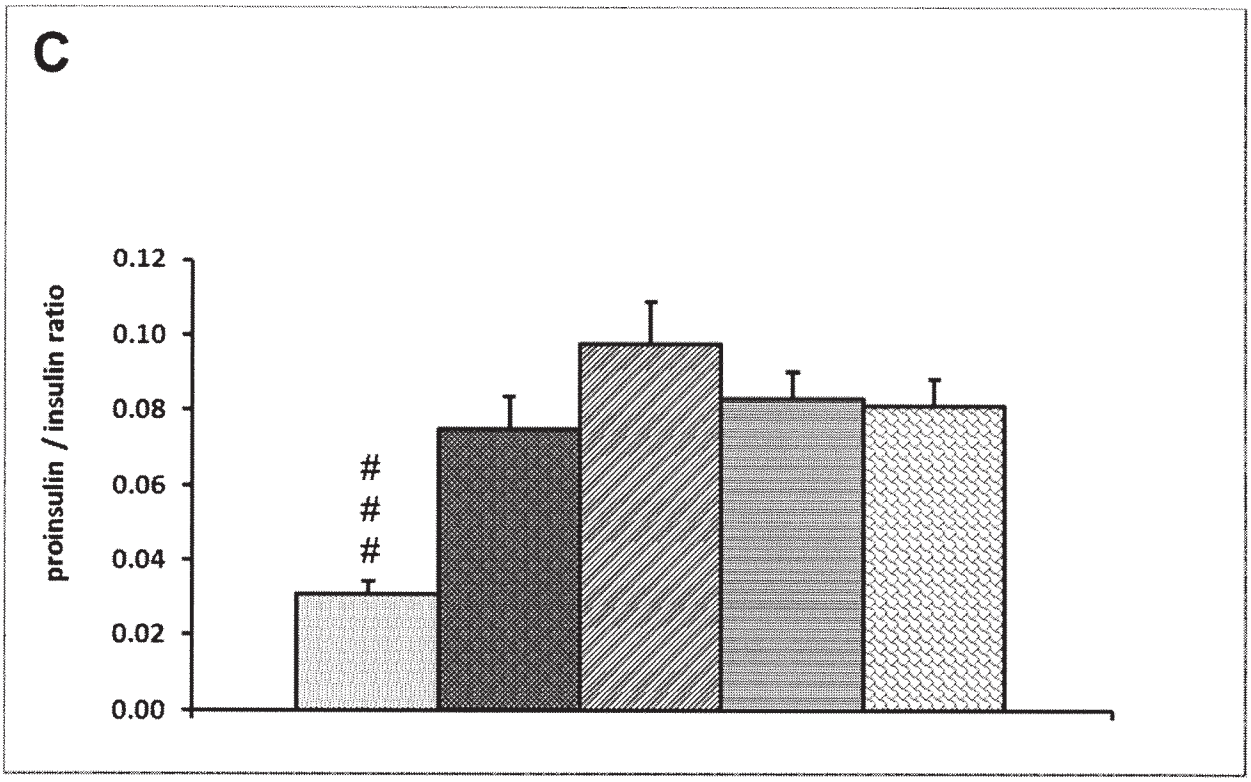


FIG. 31

