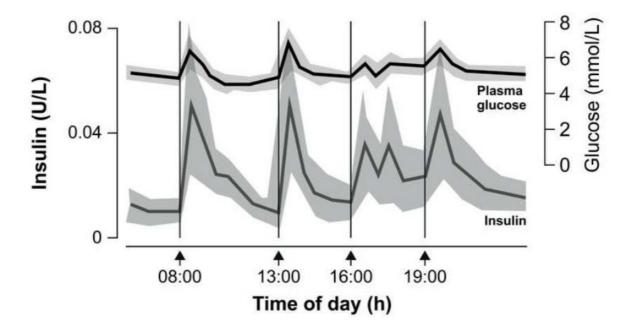
## **Supplemental Material**

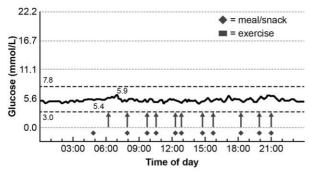
**Fig. S1** 24-hour plasma glucose and insulin profiles in healthy individuals (reprinted with permission from David Owens).



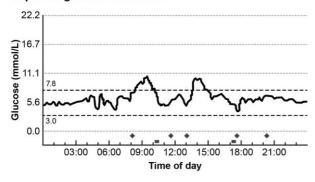
**Fig. S2** Progressive impairment of homeostatic mechanisms during development of T2DM. **a** Progression of impaired glucose tolerance (reprinted with permission from Markolf Hanefeld), and **b** Progression of impaired homeostatic mechanisms associated with impairment of glucose tolerance: i) plasma glucose, ii) plasma insulin, iii) C-peptide, iv) proinsulin (reprinted with permission from Markolf Hanefeld).

Fig. S2a

## Normal glucose tolerance



## Impaired glucose tolerance



## Advanced T2DM

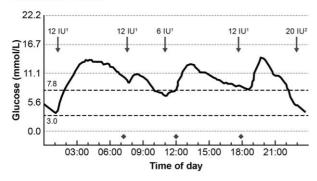
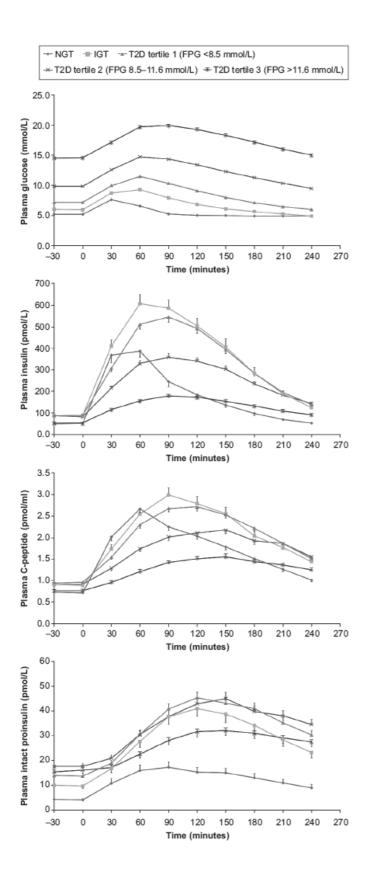


Fig. S2b



 $\begin{tabular}{ll} \textbf{Table S1} Studies of the effects of early insulin treatment on $\beta$-cell function in patients newly or recently diagnosed with T2DM \\ \end{tabular}$ 

Study type	Treatment	Patient	Treatment	Outcome
	duration	population		
Open-label	2 weeks	Severely	Short-term	Preservation of β-cell
		hyperglycemic	intensive	function at 2 years
		(n = 138)	insulin	(HOMA-B)
RCT	2 weeks	Severely	Short-term	Significant increase in
		hyperglycemic	intensive	β-cell function in both
		(n = 382)	insulin vs.	groups (HOMA-B)
			OAD	
Open-label	3 months	Relatively well	Intensive	Preservation of β-cell
intensive,		controlled (n =	insulin + OAD	function at 3.5 years (C-
then RCT vs.		58)		peptide and glucose
OAD				
Retrospective	5 months	Severely	Intensive and	Significant increase in
cohort	(mean)	hyperglycemic	non-intensive	β-cell function (HOMA-
		(n = 61)	insulin	B)
RCT	3 months	Severely	Non-intensive	Significant increase in
		hyperglycemic	insulin + OAD	β-cell function vs. OAD
		(n = 129)	vs. OAD	(HOMA-B)
Open-label	36 weeks	Mildly	Long-term	Significant increase in
		hyperglycemic	non-intensive	β-cell function vs. OAD
		(n = 75)	insulin vs.	(HOMA-B)
			OAD	
Open-label	4 weeks	Relatively well	Short-term	Significant increase in
		controlled (n =	intensive	β-cell function (ISSI-2)
		63)	insulin	
	Open-label  RCT  Open-label intensive, then RCT vs. OAD  Retrospective cohort  RCT  Open-label	duration  Open-label 2 weeks  RCT 2 weeks  Open-label 3 months intensive, then RCT vs. OAD  Retrospective 5 months (mean)  RCT 3 months  Open-label 36 weeks	Open-label2 weeksSeverely hyperglycemic (n = 138)RCT2 weeksSeverely hyperglycemic (n = 382)Open-label intensive, then RCT vs. OAD3 months controlled (n = 58)Retrospective cohort5 months (mean)Severely hyperglycemic (n = 61)RCT3 monthsSeverely hyperglycemic (n = 129)Open-label36 weeksMildly hyperglycemic (n = 75)Open-label4 weeksRelatively well controlled (n =	Open-label         2 weeks         Severely hyperglycemic (n = 138)         Short-term intensive insulin           RCT         2 weeks         Severely hyperglycemic (n = 382)         Short-term intensive insulin           Open-label intensive, then RCT vs. OAD         3 months (mean)         Relatively well controlled (n = 58)         Intensive insulin + OAD           Retrospective cohort         5 months (mean)         Severely hyperglycemic (n = 61)         Intensive and non-intensive insulin           RCT         3 months         Severely hyperglycemic (n = 129)         Non-intensive insulin + OAD vs. OAD           Open-label         36 weeks         Mildly Mildly Long-term non-intensive insulin vs. OAD           Open-label         4 weeks         Relatively well controlled (n = intensive insulin vs. OAD

HOMA-B Homeostasis Model Assessment-B, ISSI-2 insulin secretion sensitivity index, OAD oral antidiabetes drug, RCT randomized controlled trial, T2DM type 2 diabetes mellitus