Interferon-gamma increases monocyte HLA-DR expression without effects on glucose and fat metabolism in post-operative patients

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abbreviated title: IFN-gamma in surgical patients

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Abstract

Tissue injury is associated with decreased cellular immunity and enhanced metabolism. Immuno-depression is thought to be counteracted by interferon-gamma (IFN-γ), which increases human leukocyte antigen-DR (HLA-DR) expression. Hypermetabolism could be enhanced by IFN-γ since cytokines induce an hypermetabolic response to stress. In healthy humans IFN-γ enhanced HLA-DR expression without effects on glucose and fat metabolism. In the present study we evaluated whether IFN-γ lacks potential harmful side effects on metabolic and endocrine pathways while maintaining its beneficial effects on the immune system under conditions in which the inflammatory response system is activated. We studied in thirteen patients scheduled for major surgery, HLA-DR expression on peripheral blood monocytes prior to surgery and post-operatively randomized the patients into an intervention and placebo group. Subsequently, we evaluated the effects of a single dose of IFN-γ vs. saline, on short-term monocyte activation, glucose and lipid metabolism and glucose and lipid regulatory hormones.

HLA-DR expression on monocytes was restored from post-operative levels of 54%(42-60%) (median and interquartiles) to 92%(91-96%) 24 hours after IFN-γ administration, but stayed low in the placebo treated patients. IFN-γ did not effect glucose metabolism (plasma glucose, rate (R) of appearance (a) and dissappearance (d) of glucose) and lipid metabolism (plasma glycerol, plasma free fatty acids and Ra and Rd of glycerol). IFN-γ had no effect on plasma cortisol, adrenocorticotropic hormone, growth hormone, insulin, c-peptide, glucagon, epinephrine and norepinephrine concentrations. We conclude that IFN-γ exerts a favorable effect on cell-mediated immunity in patients after major surgery without effects on glucose and lipid metabolism.

Keywords: HPA-axis hormones, stable isotopes, trauma, cytokines.


**Introduction**

Tissue injury is associated with decreased expression of human leukocyte antigen-DR (HLA-DR) on monocytes (2; 15; 16; 20; 22; 37). Low levels of HLA-DR on monocytes are an ominous prognostic factor in the recovery of surgical patients, since reduced HLA-DR expression (or a defective antigen presentation or cellular immunity) is correlated with increased post-operative complications and mortality (18). Downregulation of HLA-DR expression on monocytes may partly be related to a surgically directed shift of the T-helper 1 (Th1)/Th2 balance toward a dominating Th2 type immune response (7). Compared to pre-operative production, post-operatively stimulated peripheral blood mononuclear cells (PBMC) produce significantly more Th2 cytokine interleukin (IL)-4 than its Th1 counterpart interferon-gamma (IFN-γ) (7; 24).

Administration of IFN-γ enhances the expression of HLA-DR on monocytes in vitro and in vivo (17). Several small to intermediate-sized clinical trials have addressed the effect of IFN-γ on HLA-DR expression and clinical recovery after sepsis (21) and severe injury (8; 11; 28; 38). These studies suggest that administration of IFN-γ to surgical patients could have positive effects on post-operative recovery and prevention of complications, although the data are ambiguous at present (10; 25).

In addition to the reduction in cellular immunity, another –potentially harmful- side effect of surgical interventions is the metabolic response to stress (26; 39). This response, which is characterised by catabolic reactions such as increases in glucose production, lipolysis and protein turnover, is mediated by the interaction between hormones, inflammatory mediators and the central nervous system (13; 30). Administration of inflammatory mediators like tumor necrosis factor (TNF)-α, IFN-α, IL-2 or IL-6 to humans, mimics the catabolic changes observed after tissue injury, with specific effects for each individual cytokine (4; 33; 36). In a previous study,
we administered rhIFN-γ (100µg/m², s.c.) to healthy subjects in a saline controlled cross-over study with measurements of HLA-DR expression on monocytes and endocrine and metabolic parameters (6). IFN-γ induced a profound increase in HLA-DR expression on monocytes, whereas, in contrast to other cytokines tested in a comparable setting, IFN-γ exerted surprisingly small endocrine and metabolic effects (6).

Considering these observations, IFN-γ seems to be an ideal cytokine to improve the cellular immune function in surgical patients without an additional negative influence on an activated metabolic and endocrine system. However, our observations in healthy subjects do not exclude a possible deviated endocrine and/or metabolic reaction to IFN-γ in surgical patients. For instance, IFN-γ may act synergistically with the many inflammatory response proteins that abundantly circulate in post-operative patients (9; 27; 34). The question arises therefore, whether IFN-γ also lacks harmful side effects on the metabolic and endocrine pathways under conditions in which the host inflammatory response system is activated, while maintaining its beneficial effects on the immune system. To our knowledge, no studies have been published in which acute metabolic, endocrine and immunological effects of IFN-γ administration are studied simultaneously in a homogeneous surgical patient population.

In patients, scheduled for major surgery (pylorus-preserving pancreatico-duodenectomy) we evaluated HLA-DR expression on peripheral blood monocytes prior to surgery. Post-operatively, patients were randomised into an intervention (IFN-γ) and control (saline) group. Subsequently, we evaluated the effects of a single dose of recombinant human (rh)IFN-γ (Immukine, 100µg/m², s.c.) vs. saline, on short-term monocyte activation and metabolic and endocrine parameters.
Subjects and Methods

Experimental Subjects

Between December 1998 and December 1999 twenty-four patients entered the study. All patients were scheduled for elective pylorus-preserving pancreaticoduodenectomy (pppd) aimed at curative treatment of a suspicious tumor in the pancreatic head, papilla of Vater, distal bile duct or duodenum. Exclusion criteria were: a) any other diseases than the currently treated disorder (including diabetes mellitus associated with the primary disease); b) jaundice at hospital admission (bilirubin levels >40 µmol/L, pre-operative biliary drainage was accepted); c) fever in the 2 weeks prior to hospital admission; d) any medication at admission to the hospital (except for paracetamol, pancreatic enzyme supplement or sleep medication); e) irresectability as a peroperative finding, and therefore deviation of the intended pppd procedure towards a bypass procedure; f) clinical instability or evidence of infection on the day of the study (the second post-operative day).

All patients gave written informed consent, in accordance with the Helsinki Declaration of Human Rights. The study was approved by the Research Committee and the Medical Ethical Committee of the Academic Medical Center, Amsterdam.
**Study design**

One day prior to the surgical procedure, blood was sampled for measurement of HLA-DR expression on monocytes and routine biochemical and haematological measurements (including bilirubin). From 06.00 P.M. at the pre-operative day till 05.00 P.M. at the second post-operative day, patients were only permitted to drink water in accordance with the protocol for this surgical procedure.

During surgical intervention, patients were anesthesized using isoflurane and sufentanyl supplemented with drugs provided to the discretion of the anaesthesiologist. Moreover, a high thoracic epidural catheter was inserted through which marcaine was administered. At the first post-operative day, patients were transferred from the recovery room to the general surgical ward. From 0.00 A.M. at the first post-operative day until 5.00 P.M at the second post-operative day, intravenous infusion fluids were limited to saline. Oral food supply or usage of the feeding jejunostomy was only allowed from 06.00 P.M. the second post-operative day onwards according to the treatment protocol. Analgesics were prescribed according the standard hospital protocol (paracetamol, morphine and epidural marcaine). Additionally, all patients received Fraxiparin® (Sanofi, Maassluis, The Netherlands) and Sandostatin® (Novartis Pharma Ltd. Bazel, Swiss).

On the second post-operative day patients were randomized to the IFN-γ or control group by balanced assignment. At 6.45 h A.M., a catheter was placed retrogradely into an antecubital vein for sampling of venous blood. The blood was arterialized by placement of the forearm in a thermoregulated (65°C) Plexiglas box during 20 minutes before blood was sampled. Another catheter, situated already in the contralateral hand vein or a central venous catheter -if available- was used for infusion of stable isotope tracers. Both catheters were kept patent by infusion of NaCl 0.65% (30 ml/h).
At 7.00 h A.M. blood was sampled for determination of background isotope enrichment. Subsequently, a primed (17.6 µmol/kg), continuous (0.22 µmol/kg/min) infusion of [6,6-²H₂]glucose (CIL, Andover, MA, USA) and a primed (1.5 µmol/kg), continuous (0.1 µmol/kg/min) infusion of [1,1,2,3,3-²H₅]-glycerol (CIL, Andover, MA, USA) were started and continued until the end of the first study day (t = 8 h). At t = -10, -5 min. and just before rhIFN-γ or saline administration, blood samples for determination of isotope enrichment of [6,6-²H₂]glucose and [1,1,2,3,3-²H₅]glycerol were drawn. Blood samples for baseline values of plasma hormones, substrates and cytokines and HLA-DR expression on monocytes were drawn just before rhIFN-γ or saline solution was administered. At 09.00 A.M. (t=0 h), rhIFN-γ (100 µg/m², Immukine, Boehringer Ingelheim GmbH, Ingelheim/Rhein, Germany) or a comparable volume of saline solution was injected subcutaneously in the upper leg. At 1, 2, 4, 6, and 8 h after injection of rhIFN-γ or saline, blood was drawn for the measurement of isotope enrichment, hormone, substrate and cytokine concentrations. Twenty-four and 48 hours after the injection of rhIFN-γ or saline blood was drawn for determination of plasma IFN-γ levels. Blood samples taken at 8 and 24 hours after administration of rhIFN-γ were also analysed for HLA-DR expression on monocytes. Blood pressure (Riva Rocci method, brachial artery), pulse rate (palpation of radial artery) and oral temperature (Terumo Dig. Clin. Thermometer C11, Terumo Corp., Tokyo, Japan) were recorded on the first study day at the bloodsampling timepoints.
Assays

All measurements of each individual subject were performed in the same run and tested in duplicate, with the exception of flow cytometric analysis, which was performed immediately after blood sampling.

Plasma glucose concentrations and enrichment were determined according to Reinhauer et al. (29), using xylose as internal standard. The gas chromatography column used was a J&W DB-17 capillary column (30 x 0.25 mm, d_f 0.25 µm) (J&W, Folsom, CA) on an HP 6890 Series gas chromatograph coupled to an HP 5973 mass selective detector (Hewlett Packard, Palo Alto, CA). Mass spectra were recorded at m/z 187 for glucose and m/z 189 for 6,6-²H₂-glucose. The internal standard was monitored at m/z 145. Plasma glycerol concentrations and enrichment were determined as described previously (1).

Free fatty acid (FFA) concentrations in plasma were determined using the NEFA C kit (code No 994-75409 E) from Wako Chemicals GmbH (Neuss, Germany). Plasma insulin concentration was measured by RIA (Insulin RIA 100, Pharmacia Diagnostic AB, Uppsala, Sweden; intra-assay coefficient of variation (CV) 3-5%, inter-assay CV 6-9%), C-peptide by RIA (RIA-coat c-peptide, Byk-Sangtec Diagnostics GmbH & Co. KG, Dietzenbach, Germany; intra-assay CV 4-6%, inter-assay CV 6-8%). Glucagon was determined by RIA (Linco Research, St Charles, MO; detection limit 15 ng/L, intra-assay CV 3-5%, inter-assay CV 9-13%). Cortisol was measured using a luminescence enzyme immunoassay, Immulite (Cortisol, Diagnostic Products Corporation, LA, intra-assay CV 5.8%, inter-assay CV 7.0%), adrenocorticotropic hormone (ACTH) by ILMA (Immuno Lumino Metric Assay)(Nichols Institute, Los Angeles, CA; intra-assay CV 4.3%, inter-assay CV 5.4 %, resp.), growth hormone (GH) by ILMA (Nichols Institute, Los Angeles, CA; detection limit 1 mU/L, intra-assay CV 7.3, inter-assay CV 9.6%, resp). Catecholamines were measured by in-house HPLC method. Norepinephrine (inter-assay CV 13%, intra-assay CV 6 %)
and epinephrine (inter-assay CV 14%, intra-assay CV 7%) were selectively isolated by liquid-liquid extraction and derivatized to fluorescent components with 1,2-diphenylethylenediamine. The fluorescent derivatives were separated by reversed phase liquid chromatography and detected by fluorescence detection (31; 35).

IFN-γ was measured using an in-house sandwich ELISA with a detection limit of 31 pg/ml with monoclonal antibody (mAb) MD2 as capture and biotinylated MD1 as detecting mAb, with a detection limit of 31 pg/ml. Monocyte HLA-DR expression was measured using flow cytometry as described previously (6). Cells were incubated with anti-HLA-DR monoclonal antibodies (mAbs) directly labelled with fluorescein isothiocyanate (FITC, Becton Dickinson (BD), San Jose, CA). Irrelevant mouse mAbs directly labelled with FITC (BD) were used as control for background staining. Data acquisition was performed on a FACScan flow cytometer (BD). Monocytes were gated by forward and side scatter parameters.
Calculations and statistics

Data are presented as median values with 25 and 75 percentiles. Glucose and glycerol rate of appearance (Ra, representing endogenous glucose and glycerol production), and glucose and glycerol disappearance (Rd, representing glucose and glycerol disposal) were calculated using Steele's equation for non-steady state conditions adapted for stable isotopes:

\[
R_a(t) = \frac{I}{PCT_p(t)} - \frac{pVG(t)[dPCT_p(t)/dt]}{PCT_p(t)}
\]

\[
R_d(t) = \frac{I}{PCT_p(t)} - \frac{pVG(t)[dPCT_p(t)/dt]}{PCT_p(t)} - pV \frac{dG(t)}{dt}
\]

where I is the constant tracer infusion rate (mg·kg\(^{-1}\)·min\(^{-1}\)), PCT\(_p\)(t) is the percent enrichment in plasma glucose or glycerol taken as the average of two consecutive samples, p is the pool fraction, V is the distribution volume of glucose (165 ml/kg) or glycerol (235 ml/kg), G(t) is the plasma glucose or glycerol concentration taken as the average of two consecutive samples, \(dPCT_p(t)/dt\) is the rate of change of percent enrichment in plasma (min\(^{-1}\)).

To test changes in the laboratory parameters over time within and between groups, data were analysed using analysis of repeated measures by the PROC MIXED procedure of the SAS statistical software release 8.02. Proc Mixed was used to apply analysis of repeated measures modelling fixed and random effects taking into account the covariance of the analysed variables. Except for temperature and glucagon concentrations, this statistical test was performed after logarithmic transformation of the parameters to obtain normal distribution. A p-value of < 0.05 was considered...
to represent statistical significance. Only the data from subjects who completed the entire study were used for analysis.
Results

Patient characteristics (table 1)

Initially, 24 patients were included in the study. Post-operatively, 10 patients were excluded from the study, because the tumor was irresectable with concomitant deviation of the pppd procedure. One other patient was excluded on the second post-operative day before IFN-γ/saline was administered, because of cardiac and respiratory instability. Thirteen other patients continued the study on the second post-operative day and were randomly assigned to the placebo or intervention group. Seven patients received 100 µg/m² rhIFN-γ subcutaneously, whereas 6 other patients received a similar volume of isotonic saline. Clinical characteristics of these patients are given in table 1.
Clinical effects of IFN-γ

In both study arms the incidence of clinical symptoms as chills, nausea and headache was comparable. There were no differences between the two study arms in baseline body temperature, which were 36.9 °C (36.5-37.6 °C) and 37.3 °C (36.7-37.5 °C) for the IFN-γ group and control group, respectively. In both groups there was a small though statistically significant increase in body temperature (p=0.002), which was highest in the IFN-γ group [p=0.053, at t=8 hours, 38.3 °C (37.5-38.3 °C)]. During hospital admission one patient in each group suffered from an infectious complication, but recovered after treatment with antibiotics.
Pre-operative and baseline IFN-γ levels fluctuated around the lower limit of detection of our assay (31 pg/ml). During the control study, no changes from baseline levels were detected. After injection of rhIFN-γ, IFN-γ serum levels gradually increased to a peak level of 108 pg/ml (90-127 pg/ml). Twenty-four hours after rhIFN-γ administration, IFN-γ levels were back to baseline.
Monocyte activation (fig. 1).

HLA-DR: Pre-operatively, HLA-DR expression on peripheral blood monocytes in the 13 patients who completed the study, was 94% (91-96%). On the second post-operative day, just prior to injection of IFN-γ, monocyte HLA-DR expression decreased to 54% (42-60%) and 39% (37-47%) for the intervention and control study, respectively. This decrease did not differ between the two groups. After the intervention, the monocyte HLA-DR expression did not change over time in the control group (p=0.13), whereas in the IFN-γ group the monocyte HLA-DR expression increased to 92% (91-96%) at t=24 hours (p<0.0001), which was different from the control group (p<0.001).
Hormones (table 2)

There were no differences between the two groups in baseline levels of ACTH, cortisol, insulin, C-peptide, glucagon, growth hormone, epinephrine and norepinephrine. After IFN-γ/saline administration, there were no significant changes in hormone levels within the groups and no differences were measured over time between the groups.
Substrates of energy metabolism and glucose and glycerol kinetics (fig. 2 and 3)

Glucose: Baseline values of glucose Ra and Rd of glucose did not differ between the 2 study groups. There was no effect of IFN-γ on plasma glucose levels and there were no differences measured in time between both study groups. There was a significant decline, which was most marked in the first study hour, in both Ra and Rd of glucose in the IFN-γ and control groups (p=0.0001, change within group for both Ra and Rd after IFN-γ), whereas there were no differences over time between the IFN-γ and control group.

Fat: Baseline values of plasma FFA, plasma glycerol, Ra and Rd glycerol did not differ between the two study groups. There was no effect measured in time on plasma FFA and glycerol levels within the groups, nor between the groups. For Ra and Rd glycerol levels there was no effect of IFN-γ in time within the group, although there was a significant difference in time between the IFN-γ and control group (p<0.05 for both Ra and Rd of glycerol).
Discussion

In the present study, we evaluated in post-operative patients, the short term effects of IFN-γ on immunological, endocrine and metabolic parameters. The surgical intervention induced a reduction of monocyte HLA-DR expression, that was restored by IFN-γ. IFN-γ did not induce effects on plasma glucose levels, glucose turnover or glucoregulatory hormone concentrations. Moreover, IFN-γ had no effect on parameters of lipolysis. Therefore, similar to results obtained in healthy volunteers (6), IFN-γ induced no significant metabolic effects in surgical patients. Finally, a single dose of IFN-γ (100 µg/m²) did not induce significant clinical side effects in these post-operative patients.

The present study is the first study in which pre-operative and post-operative levels and the effects of IFN-γ administration on HLA-DR expression on monocytes were measured in one combined study. Enhanced levels of HLA-DR expression on monocytes after IFN-γ injection compared to controls have been described previously in post-operative patients with colon cancer, severely injured patients and in septic patients (21; 23; 40). In contrast to the present study, in none of these studies there were measurements performed prior to (elective) trauma or the disease. In the patients with colon cancer, IFN-γ treatment (200 µg/d) was started 3 to 4 weeks after curative elective surgery and HLA-DR expression was measured after 1 month of treatment (40). In these patients HLA-DR expression increased from 88% at baseline to 97% after 1 month of treatment, whereas post-operative HLA-DR expression stayed low in the control group during the total follow-up period of 12 weeks. In trauma patients, receiving IFN-γ (100 µg/day), HLA-DR levels on monocytes prior to treatment with IFN-γ were 57% and increased to 76% after two days of treatment with IFN-γ (23). In septic patients, HLA-DR expression on monocytes prior to treatment was 27% and IFN-γ (100 µg/d) increased HLA-DR expression to 62% within 24 h (21). Our patients presented with HLA-DR expression levels after surgery that were intermediately reduced (50% 2nd
day post-operative), but reached higher levels of expression 24 hours post IFN-γ (93%). In all these studies including our own, IFN-γ clearly increased HLA-DR expression, reflecting a significant recovery of monocyte function. The effect of exogenous IFN-γ on monocytes in post-operative patients was obtained despite significantly lower peak levels in plasma IFN-γ compared to our healthy subjects (6). Since the dose of IFN-γ was equal in both studies, it must be concluded that the clearance of IFN-γ is increased after surgery, a finding that has also been described for other mediators like insulin (5).

Cytokines are thought to play an important role in the metabolic response to injury (39). Administration of cytokines like TNF-α, IL-6 and IFN-α in humans induces an hypermetabolic state, which is reflected by cytokine-specific elevations in resting energy expenditure and increases in glucose and glycerol turnover (4; 33; 36). IFN-γ, commonly marked as an important pro-inflammatory cytokine, was regarded to have a comparable effect on hormones and metabolism (3). In healthy humans, however, IFN-γ only induced a limited increase in REE and did not affect glucose metabolism (6). Again, in the present study in surgical patients, IFN-γ induced no significant effects on endogenous glucose production or glucoregulatory hormone levels as compared to saline administration. The initial decline in both Ra and Rd of glucose in the intervention and control studies, seems not to be mediated by glucoregulatory hormones, since no changes from baseline hormone levels were observed. Therefore, the phenomenon which might be a postoperative effect of the surgical procedure, is possibly mediated by paracrine factors or the neuroendocrine system. In addition, in the present study, IFN-γ also lacked a clear effect on lipolysis. The difference in Ra and Rd of glycerol in time between the IFN-γ and control group is probably due to relatively high baseline levels in the control subjects and a subsequent regression to the mean during the study within this group. This consideration is based on recent data from our research group. In patients that
underwent major surgery as treatment for oesophagus cancer (measurements on the 2nd post-operative day, n=11), Ra levels were very comparable to those of the IFN-γ group: 3.5 (2.7-4.0) µmol/kg/min (P.H. Bisschop et. al., not published). This explanation seems to be more attractive than a possible IFN-γ induced block that prevents a surgery induced decrease in Ra and Rd of glycerol. To our knowledge there are no data (in vitro and in vivo) that describe a IFN-γ induced decrease of lipolytic parameters: on the contrary, in vitro relatively high dosages of IFN-γ would increase lipolysis in cultured adipocytes(12). However, our observation that IFN-γ does not effect lipolysis in surgical patients, is in agreement with our data obtained in healthy volunteers, in which IFN-γ did not affect FFA plasma levels (6) nor Ra glycerol (de Metz, unpublished data). Therefore, IFN-γ does not seem to be an important mediator of fat metabolism in humans.

Previous human studies reported the effects of IFN-γ on HPA-axis activation. Increased cortisol release was unanimously found in these studies, whereas data on modulation of ACTH release are contradictory (6; 14; 19; 32). The studies in which no ACTH increase was measured preceding a cortisol peak suggest the possibility of an ACTH-independent effect of IFN-γ on the adrenal glands (19; 32). In the present study no effects of IFN-γ on ACTH or cortisol levels could be detected. High baseline cortisol levels in post-operative patients may explain this lack of IFN-γ effect on plasma cortisol levels. The absence of an effect on ACTH in the present study may be due to the absence of an effect of IFN-γ on the mediator which could account for ACTH release in the previous studies: plasma IL-6, a known stimulator of ACTH release (33).

It cannot be deduced from our study to what extent IFN-γ administration will result in improvement in clinical outcome. In 3 randomised trials IFN-γ administration to severely injured (trauma/burn) or sepsis patients did not result in definitive improvement in clinical relevant
endpoints. Nevertheless, there is reason to believe that high risk patients might benefit from adjuvant IFN-γ therapy (10; 11; 28; 38).

We conclude that IFN-γ exerts a favourable effect on cell-mediated immunity in patients after major surgery. Moreover, in surgical patients IFN-γ does not have measurable clinical, endocrine or metabolic side effects.

Acknowledgements

We would like to thank the Laboratory of Endocrinology for excellent analytical support. Furthermore we would like to thank Richard Reijneke and Frank van Diepen for their skilful technical assistance. J.A. Romijn is supported by the Netherlands Organisation for Scientific Research (NWO) and the Dutch Diabetes Foundation.
References


Figure legends

**Fig. 1.**  
Effects of interferon-gamma (IFN-γ) vs. saline on the percentage of human leukocyte antigen-DR (HLA-DR) positive monocytes in surgical patients. Pre-operative (pre O) and post-operative (post O) data are separated by the dashed line. Post-operative samples were taken just prior (0) and 8 and 24 hours after the administration of 100 µg/m² rhIFN-γ (closed bars, n=7) or saline (open bars, n=6). Data are expressed as medians (bars indicate the 25 and 75 percentiles). Post-operatively, monocyte HLA-DR expression did not change over time in the control group (p=0.13), whereas in the IFN-γ group monocyte HLA-DR expression increased (at t=24 hours; p<0.0001), which was different from the control group (p<0.001).

**Fig. 2**  
Effects of interferon-gamma (IFN-γ) vs. saline on glucose metabolism. Plasma glucose concentration and rate of appearance (Ra) and of disappearance (Rd) of glucose after 100 µg/m² rhIFN-γ (closed circles, n=7) or saline (open circles, n=6) administration to post-operative patients. Data are expressed as medians (bars indicate the 25 and 75 percentiles).

**Fig. 3**  
Effects of interferon-gamma (IFN-γ) on fat metabolism. Plasma free fatty acids (FFA) and glycerol concentration and the rate of appearance (Ra) and disappearance (Rd) of glycerol after 100 µg/m² rhIFN-γ (closed circles, n=7) or saline (open circles, n=6) administration to post-operative patients. Data are expressed as medians (bars indicate the 25 and 75 percentiles).
Table 1:

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<td><strong>age</strong></td>
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<td>(years)</td>
<td>63 (57-73)</td>
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<tr>
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<tr>
<td>(kg/m²)</td>
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<tr>
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<tr>
<td>(minutes)</td>
<td>315 (298-368)</td>
<td>283 (250-330)</td>
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<tr>
<td><strong>hospital stay</strong></td>
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<tr>
<td>(days †)</td>
<td>10 (9-25)</td>
<td>15 (14-19)</td>
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Data are expressed as counts (sex) or median values and 25 and 75 percentiles. No significant differences were detected between the groups. †; counted from the first postoperative day. IFN-gamma: interferon-gamma; BMI: Body Mass Index.
Table 2.

<table>
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<tr>
<td>ACTH ng/L</td>
<td>8 (5-22)</td>
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<td>cortisol nmol/L</td>
<td>540 (360-580)</td>
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<td>c-peptide pmol/L</td>
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<td>glucagon ng/L</td>
<td>65 (55-125)</td>
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<td>1.65 (1.47-5.46)</td>
<td>1.52 (0.86-2.62)</td>
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<td>growth hormone mU/L</td>
<td>2.4 (1.3-2.9)</td>
<td>1.8 (0.6-3.0)</td>
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Hormone levels on the 2nd post operative day, just prior to IFN-gamma or saline (placebo) administration

Data are expressed as median values and 25 and 75 percentiles

No significant differences were detected between the groups

IFN-gamma: interferon-gamma; ACTH: adrenocorticotropic hormone;
Fig. 1

![Graph showing HLA-DR expression on monocytes](image-url)
Fig. 2
Fig. 3

![Graphs showing changes in FFA (mmol/l), glycerol (µmol/l), Ra glycerol (µmol.kg\(^{-1}\).min\(^{-1}\)), and Rd glycerol (µmol.kg\(^{-1}\).min\(^{-1}\)) over time (hours).]