for G- CSF–induced mobilization was approved by the local ethics committee, was conducted in accordance with the Declaration of Helsinki as revised in 2000 and is registered at ClinicalTrials.gov (NCT01102699).
RESULTS: In vitro, PPAR-γ activation with pioglitazone switched both human and mice macrophages polarization from M1 to M2, reduced Osm expression, and prevented trans-cellular induction of Cxcl12 on stromal cells by macrophages-conditioned medium (Fig. 1A-E). In diabetic mice, pioglitazone treatment downregulated Osm, p66Shc, and Cxcl12 in the hematopoietic BM, restored the effects of G-CSF, and partially rescued HSPC mobilization, but it increased BM adipocytes (Fig. 1F-H). Using Osm-/- mice, we could show that Osm deletion recapitulated the effects of pioglitazone on adipogenesis, which was p66Shc independent, and double knockout of Osm and p66Shc completely rescued HSPC mobilization (Fig. 1J). In the absence of OSM, BM adipocytes produced less CXCL12, being arguably devoid of HSPC-retaining activity, whereas pioglitazone failed to downregulate Cxcl12 in BM adipocytes. In patients with diabetes on pioglitazone therapy, HSPC mobilization after G-CSF was partially rescued (Fig. 1H).
CONCLUSIONS: Pioglitazone reprogrammed BM macrophages and suppressed OSM signaling, but sustained Cxcl12 expression by BM adipocytes could limit full recovery of HSPC mobilization in diabetic animals and patients.

SEX DIFFERENCES ON MITOTANE CONCENTRATION AND TREATMENT OUTCOME IN PATIENTS WITH ADRENOCORTICAL CARCINOMA

(1) Sarah Allegra, (2) Soraya Puglisi, (1) Irene Brescia, (1) Francesco Chiara, (2) Vittoria Basile, (2) Anna Calabrese, (2) Giuseppe Reimondo, (1) Silvia De Francia

(1) Department of Biological and Clinical Sciences, Laboratory of Clinical Pharmacology "Franco Ghezzo", S. Luigi Gonzaga Hospital, University of Turin, Orbassano (TO), Italy
(2) Internal Medicine, Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital, University of Turin, Orbassano (TO), Italy

BACKGROUND: In clinical settings, data regarding sex are rarely investigated. In women, factors as body size and composition, hormonal variations, metabolism and access to care systems and therapy, could strongly influence the pharmacological management and the outcome of treatments. To underline this sex-related difference, we retrospectively collected data of adrenocortical carcinoma patients treated with mitotane, and then we evaluated sex-related pharmacokinetics parameters.
METHODS: A fully validated chromatographic method was used to quantify mitotane concentration in plasma collected from adult patients, also considering the active metabolite o,p'-DDE. Statistical analyses have been used to evaluate the sex influence on drugs pharmacokinetics.
RESULTS: We found that sex resulted as predictive factor of plasma mitotane and o,p'-DDE concentrations and significantly influenced the achievement of the therapeutic target of mitotane, implying that female sex could be a risk factor of treatment failure.
CONCLUSIONS: These results suggest that mitotane therapy should be modulated according to patient sex. Furthermore, the proposed approach could contribute to facilitating and disseminating sex-specific pharmacology.